# Experience and challenges of care of post kidney transplant patients in a resource poor non-transplant center

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**Background:** In recent times a number of privileged end stage kidney disease patients from the sub-Saharan African countries embark on off-shore kidney transplant to other continents, mostly India. Non-transplant renal units in the region are increasingly faced with the long term care of such patients with inherent challenges. We present our experience and challenges of providing care for such patients at the University of Port Harcourt teaching hospital in Nigeria.

**Objective:** To determine the outcomes and challenges of care of off-shore live-donor post-transplant patients in a non-transplant center.

**Methods:** Retrospective analysis of the clinical data of all post- kidney transplant patients from 2000 to 2015 was done.

**Results:** Twenty live-donor post-transplant patients with M/F ratio of 3:1 and a mean age of 42.6 ± 8.3 (26-57) years were studied. 95% had their kidney transplant in India. Mean pre-transplant e-GFR was 8.4 ± 2.4 mls/min/1.73 $m^2$ while at point of entry, post-transplant was 72.6 ± 29 ml/min/1.73 $m^2$ ($p<0.001$).

The commonest complication was graft dysfunction in 9 (45%). Others were NODAT 2 (10%), Polycythaemia 2 (10%), Sepsis, lower gastrointestinal haemorrhage and tuberculosis 1 (5%) each, respectively.

Overall mortality was 10 (50%). 1-year survival (100%), 3-year survival (45%), 5-year survival (15%) and 10-year survival (5%). The longest survivor (alive) is 15 years post- transplant. There was no significant survival difference between biologically related and non-related donors ($p>0.5$).

**Conclusion:** The overall outcome of post-transplant patients in our centre is poor. There is need for capacity building of non-transplant renal units in resource poor jurisdictions, to provide more effective care for post-transplant patients and ensure better long term outcomes.

Key Words: Post transplant care, Non-transplant center, Challenges.

## INTRODUCTION

Kidney transplant is the gold standard therapy for patients with end stage renal disease (ESRD). The global incidence and prevalence for kidney transplantation is on the increase due to rising prevalence of ESRD globally, especially in the developing countries [1,2]. Currently well over half a million people world-wide are living with kidney grafts [1,3]. In advanced countries the protocol of care of kidney transplant patients (pre and post-transplant) is well standardised, according to internationally accepted clinical care guidelines [4]. In the low- and middle-income countries (LMIC) of Latin America, Asia and middle east, transplant activities are also on the increase with current average annual transplant rates ranging from 5 to13 per million population(pmp) [5,6].

In some of these LMIC countries however, the protocol for live-donor selection and peri- operative care may not be as stringent and as highly ethical as in Europe and N. America, due to reasons of pressure of demand by desperate patients and relatives, relative deprivation of the target population, as well as for pecuniary reasons. This is inspite of the declaration of Istanbul in 2008 [7] on the ethics of kidney transplantation. In most of these populations live-donor transplants are more prevalent promoted by high frequency of trafficking and transplant tourism [8,9].

In resource poor sub-Saharan African countries like Nigeria (with the exception of South Africa) access to kidney transplant is very low as is access to maintenance dialysis [2,5]. Only Sudan has a durable kidney transplant regime due to government free transplant service. Most of the rest of the sub-Saharan African countries have no structured nor durable kidney transplant program. In Nigeria a number of university teaching hospitals had in the past attempted live-donor kidney transplants with few isolated successes. Due to poor infrastructure and lack of sustenance, the programs fizzle out soon. Only one private hospital in Nigeria has had a modest and sustained experience in live-donor kidney transplants, with about 115 transplants done within a period of twelve years [10] Because it is a private fee for service facility, the cost of transplant is perceived to be high by the public.

For reasons of lack of access and the relatively high cost in the only private facility, most Nigerian ESRD patients and relatives, who could source funds for live donor transplant, tend to flock to India and some Asian hospitals for kidney transplant. About three months after successful transplant such patients were often referred back to Nigeria, for subsequent long term post-transplant care. They are either referred back to their source hospital or a teaching hospital of close proximity.

We report below our center experience and challenges of care of these off-shore post-transplant patients who returned to our center in the past fifteen years (2000 to 2015). The renal unit of university of Port Harcourt teaching hospital is an integral part of the department of medicine, with four consultant nephrologists, assisted by senior nephrology residents. The unit has four functional haemodialysis machines, trained dialysis nurses and a dialysis technologist. The unit runs weekly renal clinic where all CKD and post-transplant patients are seen. The unit is not yet a kidney transplant center.

**Objectives:** To highlight the experience and challenges of clinical care of post-kidney transplant patients in a resource poor non-kidney transplant centre, to determine common complications, graft and patient survival in post-kidney transplant patients in our center.

**Study design:** Retrospective systematic cohort analytical study.

## PATIENTS & METHODS

Between 2000 and 2015 a cohort of patients who developed end stage kidney disease (ESRD) and subsequently had the benefit of live-donor kidney transplantation either off-shore or in Nigeria, came under our clinical supervision post- transplant. Most of the patients were registered ESRD patients who were referred from our center for transplant, while a

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few were sent for transplant from other medical centers. Post-transplant, they were referred to us for reasons of primary source or proximity to place of residence. All patients had their immediate post-operative care and about three months post-transplant care at their transplant centers, before returning to Nigeria. They usually return with about three months stock of immunosuppressive drugs, other relevant medications and a summary referral letter.

At entry each patient was duly registered in our renal clinic which hold once weekly. All relevant information from the patient's referral letter are recorded in the patient's clinical case records. Key among these are immediate pre-transplant laboratory and other investigation parameters, donor characteristics, and donor preparations (where available), record of immediate peri-operative patient parameters, information about any immediate peri-operative complications, as well as patient parameters in the months before leaving the transplant center. The list and dosages of immunosuppressive agents as well as other medications the patient is prescribed at discharge from the transplant center were recorded.

At the first encounter, patients had their baseline clinical and laboratory parameters determined. These include detailed physical examination with emphasis on cardiovascular, respiratory and urogenital systems. The transplant kidney is palpated for size, tenderness and warmth.

Baseline laboratory investigations include: urine examination, hematologic indices, biochemical indices such as electrolytes, plasma concentrations of urea, creatinine and uric acid, serum calcium, inorganic phosphates, lipid profiles and liver function tests including total proteins and albumin determinations. Cockroft and Gault [11] equation was used to determine the graft e-GFR. Also baseline plasma trough (Co) and peak levels (C2) of either ciclosporin or tacrolimus as the case may be, were requested for. Between the first and the second visit, the patients continued with their medications in the doses prescribed by the transplant center except, there were important issues necessitating alteration.

Patients were seen again within one week of the first visit, weekly for the next 8 weeks, twice monthly for the subsequent three months and monthly subsequently. Patients were advised not to wait for their next appointment date if issues arose. In the event of any emergency they were advised to report to the haemodialysis unit which operates 24- hour service with a full complement of renal unit doctors. The patients' clinical case files are domiciled in the haemodialysis unit's mini -medical records for ease of access.

For all subsequent clinic visits, patients reports with a fresh report of urine examination, complete blood count, plasma concentrations of electrolytes, urea and creatinine, uric acid. The e-GFR was recalculated to track graft function. Any fresh complaints were recorded. These include fever, oliguria, haematuria, body swelling, pains around the grafts, etc. Biophysical parameters were recorded and physical examination conducted including gentle palpation over the graft for warmth and tenderness. The new laboratory parameters were compared with the previous values for detection of any changes. Plasma levels of tacrolimus or Ciclosporin were ordered once every 8 weeks for determination of adequacy of immunosuppression. At each visit features of complications such as general and opportunistic infections and cancers, new onset diabetes mellitus, post- transplant lympho- proliferative disorders (PLTD), graft dysfunction and cardiovascular disorders were actively searched for and recorded.

Graft dysfunction and graft failure were diagnosed in accordance with KDIGO guidelines for the diagnosis and management of dysfunction of transplant kidney 4 but, with modifications, based on available local diagnostic capability. Feature of graft dysfunction sought for include, presence of new urinary abnormalities, such as active urinary sediments, leucocyturia, increased pus cells, microscopic haematuria, proteinuria, oedema, rising blood pressure and rising azotemia. An increase of the serum creatinine level to>1.5 to 2 fold from baseline or a significant drop in the e-GFR from baseline was diagnosed as graft dysfunction, while graft failure or loss was diagnosed if the graft e-GFR is<15 mls/min/1.73 $m^2$.

New onset diabetes mellitus after transplantation (NODAT) was diagnosed in accordance with the Expert committee and the American Diabetic Association (ADA) criteria for diagnosis of diabetes [12,13]. A fasting blood glucose level of>7.8 mmol/l or a 2 hr post -prandial blood glucose>11.1 mmol during two consecutive visits in a previously non-diabetic patient. New onset hypertension was diagnosed if consecutive measures of blood pressure readings were>140/90 mmHg in accordance with JNC-7 [14] from baseline in a previously non-hypertensive patient. Other complications were diagnosed based on KIDOGI clinical practice guidelines4 with local modifications.

At the earliest sign of graft dysfunction patients were investigated for possible causes and measures taken to ameliorate or reverse the situation while, arrangements were made to return the patient to the transplant centre if dysfunction continues to deteriorate in spite of intervention. Such interventions include: aggressive treatment of any inter-current/ opportunistic infections, stricter control of blood pressure, modifying doses of angiotensin converting enzyme inhibitors (ACEI) angiotensin receptor blockers (ARB's) for control of hypertension and proteinuria. Where calcineurine induced renal injury was suspected the dose of the drug was either reduced or the drug withdrawn and replaced with calcineurin-free combinations. Where inadequate immunosuppression was suspected the doses of immunosuppressive agents were stepped up. Where acute rejection is suspected, patients were placed on a salvage protocol in accordance to guidelines for management of acute rejection [4] followed by maintenance therapy, modified according to locally available agents.

These include an initial intravenous methyl prednisolone for three days and mycophenolate moefetil (MMF) regimen, followed by maintenance high doses of oral prednisolone and MMF. Where dialysis becomes indicated patients were given sessions of haemodialysis to stabilise them or are reversed back to maintenance haemodialysis as the case may be. As soon as it became feasible, the patient was referred back to the transplant center for further evaluation and care.

For the purposes of this study a structured profoma data sheet was developed to capture relevant data for each patient for subsequent collation and analysis.

## Data management

Data were analysed with the aid of statistical package for biomedical data SPSS version 17.0. Continuous variables are presented as mean ± standard deviation. Pearson's correlation coefficient was used to establish relationship between parametric variables. Student t-test was used to measure probability and significant levels in a two-tailed test. Significant levels were set at 0.05. Tables and charts were used as appropriate.

## Study limitations

The study suffers the limitations of a retrospective study in the possible inability to retrieve all data. There were limitations plasma calcineurine-inhibitor drug level assays, hence inability to determine adequacy of immunosuppression. Also, definitive histo-pathologic diagnosis of graft dysfunction or failure was not possible. Definitive diagnosis of certain opportunistic infections was not possible due to local unavailability of relevant serologic tests.

## RESULTS

During the period under review from 2000 to 2015, twenty patients who had live-donor kidney transplant outside our center, came under our care post-transplant. They were 15 males and 5 females (M/F=3:1). Their ages ranged from 26 to 57 years with a mean age of 42.6 ± 8.3years.

The major primary renal disorders causing ESRD in the patients were chronic glomerulonephritis (CGN) 8(40%), hypertensive nephrosclerosis (HTN) -5(25%), Diabetic nephropathy(DN) 3-(15%), renal cortical necrosis complicating severe peri-partum haemorrhage-2(10%), Autosomal dominant polycystic kidney disease(ADPKDS), Sickle cell nephropathy(SCN) contributing one case(5.0%) each.

End stage renal disease (ESRD) was the indication for kidney transplant in all the patients. The duration of ESRD before transplant ranged from 1 to three years with a mean of 1.7 ± 0.5 years. The pre-transplant mean e-GFR of the patients was 8.4 ± 2.4 (4.6-15.7) mls/min/1.73 $m^2$.The details of the other parameters are shown in Table 1. All the patients were on maintenance haemodialysis for varying periods of times before travelling out for kidney transplant.

For all the patients pre-transplant haemodialysis exposure was sub-optimal due to financial challenges. Due to problems of severe anaemia, most of the patients had exposure to multiple blood transfusions pre-transplant. For same reason of financial constraints exposure to erythropoietin stimulating agents (ESA) was sub-optimal. Also most of the patients solicited financial support to enable them access kidney transplantation. The distribution of the source of funds for kidney transplant was as follows: Family sources alone 5 (25%), family source & philanthropic support 14 (70%) and Government sponsorship 1 (5%).

Nineteen patients (95%) had transplant done in various hospitals in India, while one patient (5%) had kidney transplant in a Nigerian private hospital. All had live-donor transplant with donor distribution as follows: first degree relative-5 (25%), second degree raltive-2 (10%), spousal donor-2 (10%) and unrelated donors 11 (55%), respectively. All the patients had their immediate and early post-transplant recovery period of up to the first three months at the transplant center. At departure back to Nigeria, they were usually given three- month's stock of their immunosuppressive drugs and other relevant medications.

**Table 1. Profiles of the post kidney transplant patients**

| S/no | Name | Age | Sex | Year of tx. | Site of Tx | Donor | Follow-up | Notable complications | Current Status | Year of graft loss | Year of death | Duration of graft/ patient (Yrs) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *AE | 40 | F | 2000 | India | Twin sister | Good | NODAT | Alive/well | Functional | Alive | 14 |
| 2 | #AM | 56 | M | 2005 | India | Wife | Good | ACS | Died | Functional At death. | 2011 | 6 |
| 3 | *IF | 26 | F | 2008 | India | Brother | Good | NIL | Alive/well | Functional | NA | 6 |
| 4 | #AM | 40 | M | 2007 | India | Wife | poor | Graft failure | Died | 2012 | 2012 | 5 |
| 5 | #AG | 42 | M | 2006 | India | Unknown | poor | Graft failure | Died | 2009 | 2009 | 3 |
| 6 | #IG | 57 | M | 2008 | Nigeria | Cousin | poor | Graft failure | Died | 2010 | 2010 | 2 |
| 7 | #HO | 40 | M | 2009 | India | Unknown | poor | Graft failure | Died | 2011 | NA | 1.5 |
| 8 | *PS | 38 | F | 2009 | India | Brother | good | none | Alive/well | Functional | NA | 5 |
| 9 | **E K | 27 | F | 2009 | India | Unknown | poor | Graft failure | Alive/Back to dialysis. | 2012 | NA | Graft loss-3yrs./ Alive-5yr |
| 10 | !OM | 54 | M | 2010 | India | Nephew | good | GI-Haemorrhage, Nodat | Died | Functional at death | 2011 | 1.5 |
| 11 | #KS | 34 | M | 2011 | India | Brother | poor | Graft failure | Died | 2012 | 2013 | 1.5 |
| 12 | #NB | 33 | F | 2010 | India | Unknown | good | Graft failure | Died | 2012 | NA | 2 |
| 13 | *JD | 28 | M | 2012 | India | Brother | good | nil | Alive/well | Functional | NA | 2 |
| 14 | *AA | 54 | M | 2012 | India | Unknown | good | Nil | Alive/well | Functional | NA | 2 |
| 15 | *BS | 45 | M | 2012 | India | Unknown | good | nil | Alive/well | Functional | NA | 2 |
| 16 | **AF | 22 | F | 2011 | India | Unknown | poor | Graft failure | Alive/Back to dialysis | 2013 | NA | 3 |
| 17 | *EZ | 58 | M | 2011 | India | Unknown | good | Tremors, oedema | Alive/well | Functional | NA | 3 |
| 18 | #HA | 36 | M | 2010 | India | Unknown | poor | Graft failure | Died | 2012 | 2012 | 2 |
| 19 | !BG | 48 | M | 2011 | India | Unknown | good | Tuberculosis | Died | Functional At death. | 2014 | 3 |
| 20 | *AG | 57 | M | 2014 | India | Unknown | good | None | Alive | Functional | NA | 1.5 |

NODAT: New Onset Diabetes; ACS: Acute Coronary Syndrome; ESRD: End Stage Renal Disease. *Died with functional graft; **Graft failure, back to maintenance haemodialysis. NA-Not applicable. Tx-transplant.

Summary of outcomes (N=20)

*Alive with functioning graft- 8 (40%)

**Alive with failed graft: back to dialysis-2 (10%)

#Died due to failed graft -7 (35%)

!Died with functional graft-3(15%)

At entry the distribution of their immunosuppressive drug status were Cyclosporine based combination-11 (55%) while, Tacrolimus based combinations were 9 (45%). All the patient were on maintenance prednisolone in doses ranging from 5 to 15 mg per day. For those with hypertension and other cardiovascular risks, anti-hypertensive agents: angiotensin converting enzyme inhibitors(ACEI's), angiotensin receptor blockers (ARB's), calcium channel blockers-(CCB's), beta-adrenergic blockers-(BB), and statins were added.

Table 1 shows the panorama of the profiles of the patients. The first patient had her transplant in 2000. Her donor was her identical twin sister. The last patient had his transplant in 2014. Majority of the patients 14 (70%) had their transplant between 2005 and 2009.

Table 2 shows the mean values of key renal function parameters (e-GFR, Haemoglobin concentration, the haematocrit, blood urea and creatinine concentrations) before transplant and upon return from transplant center. The differences in the parameters where statistically significant ($p<0.001$) indicating that the grafts were reasonably functional in the first three months of transplant.

**Table 2. Pre and post-transplant mean values of renal and haematologic parameters of the patients**

| Status | Renal Parameters | | | | |
|---|---|---|---|---|---|
| | e-GFR (ml/min) | Hb (g/dl | Hct (%) | Urea (mmol/l) | Creat. (umol/l |
| Pre-transplant | 8.4 ± 2.4 | 7.3 ± 0.9 | 22.6 ± 3.1 | 37.1 ± 5.2 | 1383 ± 381.1 |
| Post-transplant | 72.6 ± 29.5 | 13.9 ± 1.8 | 42.7 ± 6.3 | 5.3 ± 2.7 | 144.4 ± 65.1 |
| p-value | <0.001 | < 0.001 | <0.001 | <0.001 | <0.001 |

During the period under our clinical supervision, patient compliance with clinic visits and medications was variable. For eight patients (40%) clinic attendance and medication compliance were rated as poor. Of the ten patients that died 7 (70%) had poor clinic attendance. The mean age of all the patients with poor clinic attendance was almost a decade lower than those with good clinic attendance (38.5 *vs.* 45.3 years) though, the difference was not statistically significant ($p<0.05$). The data for plasma trough (Co) and 2 hr peak levels (C2) of CsA and TAC were insufficient for analysis.

The notable complications observed in patients are set out in Table 3. Graft dysfunction and subsequent graft failure (45%) was the commonest complications observed in the patients. Three of cases of graft failure (33.3%) absconded from follow up only to present in graft failure, while the remaining six (66.7%) cases started off as graft dysfunction, but subsequently progressed to graft failure in spite of interventions and return to transplant center for some of them. Two of them survived and are back to maintenance haemodialysis awaiting second transplant. Incidentally, both of them were cases of renal cortical necrosis complicating severe peri-partum haemorrhage. The other seven died.

**Table 3. Notable complications in post-transplant patient**

| Complications | Number | Percentage |
|---|---|---|
| Graft dysfunction & failure | 9 | 0.45 |
| NODAT | 2 | 10 |
| Polycythaemia | 2 | 10 |
| Opportunistic TB | 1 | 5 |
| Opportunistic Genital warts | 1 | 5 |
| Sepsis & lower GI-haemorrhage | 1 | 5 |

NODAT: New Onset Diabetes After Transplant; TB: Tuberculosis; GI-Gastrointestinal.

Figure 1 shows the survival of the patients. All the patients survived the first year of transplant (100% 1- year survival). Three-year survival was 45%, 5-year survival 25% and 10-year survival was 5% respectively. The longest surviving patient has survived for 15 years. Her donor was her identical twin sister. The last patient has survived for 18 months post-transplant.

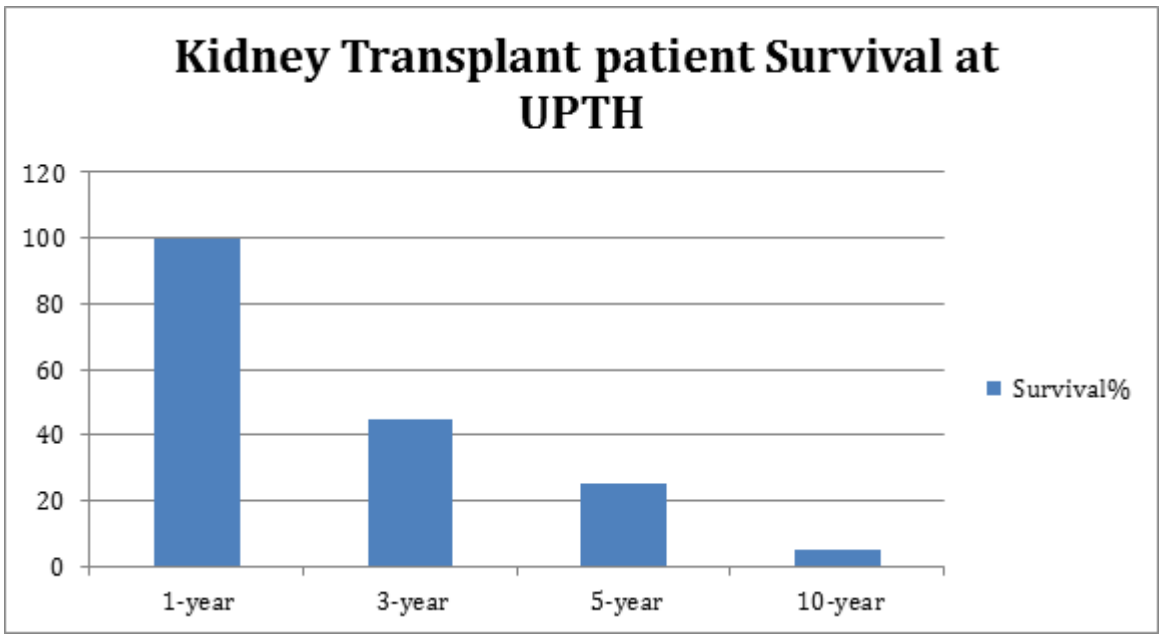


**Figure 1**. Kidney transplant patient survival

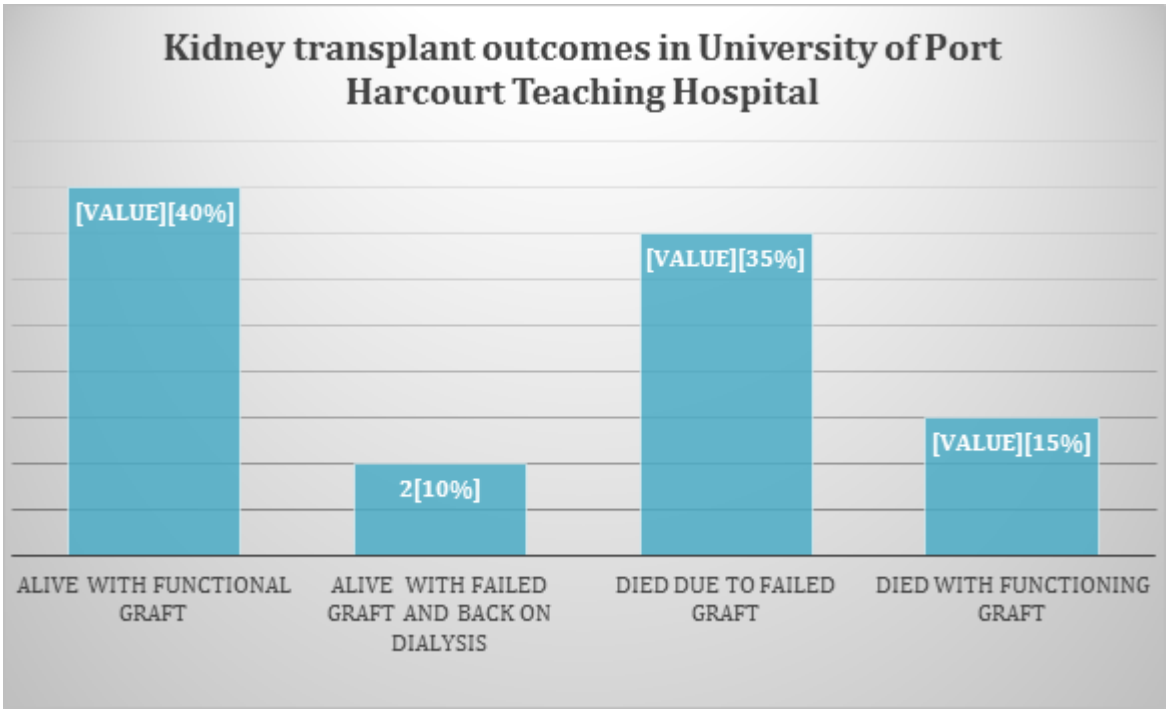


**Figure 2**. Kidney transplant outcomes in 20 patients at the University of Port Harcourt Teaching Hospital.

A cumulative total of ten (50%) patients have died. Seven of the deaths (70%) were due to graft failure and related complications. The remaining three patients (30%) died with functioning grafts from other complications; acute coronary syndrome and sepsis complicated with lower gastrointestinal haemorrhage. Of the ten surviving patients, two lost their grafts and are back to maintenance haemodialysis. The other eight patients are in varying stages of graft/ patient survival, ranging from 1.5 to 15 years. Some have visited their transplant centers on at least one occasion for check-up (Table 4).

**Table 4. Reasons for and outcomes of patients' re-visits to their transplant centers**

| S/no. | Patient (initials) | Cause of ESRD | Reason for return to transplant center | No. of visits | Outcome |
|---|---|---|---|---|---|
| 1 | AE(F/40) | CGN | Routine check | 2 | Alive |
| 2 | AM(M/56) | DN | Routine check & CAD | 2 | Died |
| 3 | IF(F/26) | CGN | | 1 | Alive |
| 4 | AM(M/40) | CGN | Routine check | 1 | Died |
| 5 | PS(F/33) | HTN | Graft dysfunction | 1 | Alive |
| 6 | NG(F/33) | Obst. haem. | Routine | 1 | Died |
| 7 | JD(M/28) | | Graft dysfunction | 1 | alive |
| 8 | BS(M/45) | SCN | Routine | 1 | Alive |
| 9 | AF(M/22) | NS | Routine | 1 | Back to dialysis |
| 10 | EZ(58)M/ | CGN | Graft dysfunction | 1 | Alive |
| | | CGN | Routine | | |

ESRD: End Stage Renal Disease; CGN: Chronic Glomerulonephritis; DN: Diabetic Nephropathy; HTN: Hypertensive Nephropathy; SCN: Sickle Cell Nephropathy; CAD: Coronary Artery Disease; Obst. haem.: Obstetric Haemorrhage.

## DISCUSSION

The patients' records show that all except one patient had their Kidney transplant in Indian hospitals. The one exception had his transplant in a private facility in Lagos, Nigeria. The mean age of the patients and the distribution of the primary kidney disorders are in keeping with data from local Nigerian and other sub-Sahran African countries for ESRD [2,15] Their mean age supports the observation that in sub-Saharan Africans, ESRD afflicts mostly people within the age band of 25-59 years, which constitute the most productive years. This is in contradistinction with Europe and North America where the median age of affectation is about 65years [16,17]. The patients' pre-transplant renal function status confirm that they were all cases of ESRD in whom kidney transplant was indicated. Also their post-transplant renal parameters at presentation to us, at about three months post-transplant, indicate that their grafts were functional for majority of the patients with a mean graft eGFR at entry of 72.6 ± 29.5 mls/min/1.73 $m^2$ (CKD-T2).

We however did not have much information about their immediate post-transplant graft performance and other peri- operative complications. We did not have information as to the incidence of delayed graft function and acute rejection episodes in the early post-operative period. Similarly we had no information of details of donor selection, and donor preparation for transplantation. With the exception of the living related donors, details of the living unrelated donors were not available.

Before travelling out for transplant, most of the patients were under-dialysed due to poor access on account of funding for maintenance haemodialysis. Most patients were on an average of one dialysis session per week which is a common pattern in most dialysis units across the country [2,18] Patients were also exposed to multiple blood transfusions due to high prevalence of severe anaemia, anaemic heart failures and acute pulmonary oedema. Such repeated blood transfusions might have exposed the patients to HLA-antigen sensitization and consequent high levels of preformed anti-lymphocyte antibodies. Blood transfusion induced HLA-antigen sensitization is a risk factor for hyper-acute and acute antibody mediated graft rejection and eventually long term graft dysfunctions [19,20].

From the post-transplant referral notes and information from the patients, only 7 (35%) of the patients had biologically related live donors. One donor was an identical twin sister, four from brothers, one each from a cousin, and nephew respectively. There were two spousal (wives) donors. The relationship with the donors in the remaining 11 (55%) patients could

not be determined. They were presumed unrelated commercial donors either procured in Nigeria (transplant tourism) or acquired offshore in India (organ trafficking). In spite of advancements in immunosuppressive protocols, the longest surviving renal grafts are often those from genetically identical twins.

The first successful live-donor kidney transplant was in identical twins [21]. The longest surviving patient in our series (15-year survival) received her graft from an identical twin sister. In our series, of the nine patients with graft failure, four of the donors were not biologically related to the recipient. Of the remaining five patients, two were spousal donors and one each of brother, cousin and nephew, respectively. The outcomes of spousal donor transplant have compared favorably with other non-related live donor transplants [22]. The low statistical power of the data would not allow for any correlation between the graft outcome and donor-recipient genetic relationship.

With the exception of graft failure, the complications profiles recorded in the patients appear to be few (Table 4). Graft dysfunction/failure was the dominant complication accounting for forty percent of complications. The relative rarity of other complications may be due to diagnostic limitations in our center. We do not have facilities for the serological confirmation of entities such as pneumocytis jirovecii (carini), Cytomegalovirus (CMV), Epstein-Barr Virus (EBV) and some other opportunistic bacterial and viral infections which are common opportunist infections in patients on immunosuppressive therapy [23,24]. Our patients however did not manifest clinical signs of any of the above infections. Also none of the patients manifested features of herpes zoster, Kaposi sarcoma, or post-transplant lympho-proliferative disease (PLTD).

Perhaps most of the patients have not survived long enough to begin to manifest these long term complications of organ transplant. The two patients who developed NODAT were counselled and commenced on insulin therapy in addition to dietary measures. The dosage of prednisolone was reduced. Unfortunately one died from non-diabetes related complications. The other is alive with good metabolic control. The case of disseminated tuberculosis and Tuberculous Meningitis (TBM) which led to his death was a case of opportunistic reactivation. Patient was treated for PTB before he travelled out for transplant. Reactivation and dissemination occurred six months post-transplant. He may not have disclosed his TB-status to the transplant center as there was no reference to TB in the patient referral notes. He was referred to India for transplant by a private commercial health organisation in Port Harcourt. He died with a functioning graft.

Reactivated latent TB is a common complication in patients on immunosuppressive therapy, HIV/AIDS patients and among substance abuse communities, in especially tuberculosis endemic environments as the SSA. KIDOGI clinical practice guidelines recommend that all maintenance dialysis patients and pre-transplant patients should be routinely screened for tuberculosis.4 Those found negative should have BCG administered. The development of QUANTIFERON TB GOLD assay for mycobacterium have improved the sensitivity for detection of TB exposure over traditional mantoux or Heaf tests, hence, a useful tool for patient and population screening [25]. There was no evidence that the patient was screened for TB before transplant at the transplant center.

The patient who died from sepsis and lower GI haemorrhagic diarrhoea, started off with post-transplant polycythaemia (erythrocytosis) with an initial haematocrit of 55%. He was also the second case of NODAT. He subsequently developed a febrile illness, the cause of which could not be readily determined despite septic work up. The polycythaemia, spontaneously dropped to normal levels and subsequently to sub-normal levels. He then developed severe bloody diarrhoea, later complicated with features of disseminated intravascular coagulation (DIC) from which he did not recover. He was on tacrolimus and mycophenilate moefetil (MMF) based maintenance immunosuppressive regimen. He died with a functioning graft. Post-transplant polycythaemia is known to occur in about 20% of post-transplant patients. Implicated causes include graft renal artery stenosis, erythropoietin production from the native kidneys as well as exaggerated bone marrow response to restored erythropoietin levels post-transplant [26].

Recommended therapies include the use of ARB's or ACEI's which are known to induced anaemia, theophylline, or repeated phlebotomies in symptomatic patients. Our patient was asymptomatic of polycythaemia and was already on valsartan (an ARB), so we did we adopted a watch and see approach. Unfortunately he developed sepsis which led to a sharp decline in haematocrit. The sepsis may have been responsible for the drastic fall in the haematocrit level. The haemorrhagic diarrhoea in this patient may also have been as a result of the MMF therapy. Haemorrhagic diarrhoea is one of the major limiting side effects of MMF therapy [27].

Though all the patients survived the first year of transplant, the subsequent survival rates for 3, 5 and 10 years were sub-optimal (Figure 2). They were worse than the survival pattern in global transplant registries, where the five and ten- year live-donor transplants survivals are of the order of 70 to 80 % and over 50%, respectively. Our patients' survival pattern were also worse than the 5- and 10- year graft survival rates for cadaveric transplants in global registries [29].

Graft dysfunction was the commonest cause of death in our patients, being responsible for 70% of the deaths. Those who died as a result of progressive graft failure died within an average of 2.3 years of transplant with a range of 2 to 5 years. The cumulative mortality rate at five years for all the patients was 75%.

Several factors may have been responsible for high rate of graft loss and death among our patients. These include possible poor donor selection by the transplant centers. Our data showed that there were more biologically related donors in the non-graft failure cohort 50% *vs.* 42.8% ($p>0.05$) than in graft failure group (Table 5). The differences were however not statistical significant and the population size was small. It is also possible that the donor renal and cardiovascular screening for risk factors of renal and cardiovascular disorders, which might affect graft function, may not have been very stringent.

Another factor may be sub-optimal immuno-suppression. Our data for calcineurin plasma drug assay were too few for objective analysis. Most of the patients were not able to regularly assay their plasma ciclosporin or tacrolimus levels for reasons of unavailability and cost. Our hospital laboratory did not have facilities for plasma calcineurine drug level assays. Patients had to be referred to a private laboratory service which, in turn sent samples to their South African mother laboratory. The results often take about a fourth night to be retrieved. The service charges were inevitably high.

It is well established that poor donor selection, HLA- incompatibilities, sub-optimal immune-suppression contribute significantly to poor graft outcomes [30]. Also patient's compliance with clinic visits and by extension adherence to medications were sub-optimal in some patients. Poor clinic follow-up may correlate with poor medication adherence while good clinic attendance was 87.5% in those alive with functioning grafts, those who died as a result of graft failure achieved 37.5% good clinic attendance ($p<0.001$). The difference was statistically significant. Also all patients with poor clinic attendance were almost a generation younger than those with good clinic attendance. The younger transplant recipients did not seem to appreciate the enormity of the problems and costs involved in ESRD /transplant as compared to the more matured recipients. The younger ones often assumed that successful transplant amount to "cure" for ESRD. This illness behavioural pattern of the young and adolescents is universal and not peculiar to kidney transplantation, but also observed in other chronic disorders in the adolescents, such as type1 diabetes, chronic seizure disorders, bronchial asthma etc [31,32]. There is need for more post-transplant counselling for young transplant recipients.

Another factor may have been occult opportunistic infections and malignancies that may have escaped our ability to detect and manage. We however consider this is unlikely in our patients. Undiagnosed occult malignancy and opportunistic infections contribute to progressive graft dysfunction and failure [33].

**Challenges of care:** Some of the challenges we faced in providing care for these off-shore post-kidney transplant patients include: Irregular availability of a wide range of immunosuppressive agents in our pharmacy and most community pharmacies. Due to low demands most

immunosuppressive agents are usually not stocked by hospital and community pharmacies within the locality. Often has to be ordered from outside. This made critical dose adjustments and drug refills by patients difficult. Patients have to rely on drug re-fills from their transplant centers with attendant foreign exchange, postal charge and delay implications, the lack of facilities for plasma calcineurine drug level assay in our hospital made it difficult to monitor plasma immunosuppressive drug levels for proper patient evaluation. The cost at a private laboratory service is prohibitive for most of the patients, we had no facilities for kidney injury biomarkers for early detection of graft dysfunction. Urinary biomarkers such as kidney injury molecule (KIM), asymmetrical dimethyl arginine (ADMA) and IL-1 and IL-6 have been used for early detection of kidney injury in the settings of AKI and allograft rejections. Though the use of biomarkers are still largely experimental, they are beginning to have clinical application in renal transplant programs in the early detection of acute and delayed graft dysfunction [34,35], the histo-pathologic confirmation of cause(s) of graft dysfunction or graft failure was problematic because of lack of a renal pathologists and unavailability of relevant immuno-histochemical stains in our anatomical pathology division. For this reason some of our patients with graft dysfunction, who could afford it, were referred back to their transplant center for graft biopsy. Only recently, one of our histo-pathologists benefitted from ISN renal histopathology training program and is currently demonstrating capacity in renal histolopathology.

## CONCLUSION

The relatively poor outcomes of our off-shore post-transplant patients can be attributable to three sets of factors viz: transplant center factors, patient factors, and care-center factors. Transplant center factors include possible poor donor selection and poor HLA-matching influenced by transplant tourism. Patient factors include poor clinic and medication adherence behaviours, while our care-center factors include the lack of capacities for immunosuppressive drug level assays, biopsy and histo-pathologic diagnosis of graft dysfunction as well as the poor stocking of immunosuppressive agents in the hospital. With the rising incidence and prevalence of ESRD in resource challenged sub-Saharan Africa countries, an increasing number of patients who are able to benefit from off-shore renal transplants would continue to pose challenge of long-term post-transplant care in non-transplant renal centers. Renal units in collaboration with their respective hospital managements, should endeavour to build capacities for adequate care of this increasing populations of patients so that hard earned transplants would survive longer, to improve the quality of life of the recipients. Such capacities have been highlighted above. Teaching and specialist hospital in SSA countries should endeavour to acquire such capabilities. The Governments of sub-Saharan African countries should take the need for development of structured and ethical organ transplant programs in their countries (which currently does not exist in many SSA countries) as a priority. This will reduce the frequency of off-shore renal transplants, in jurisdictions with relatively lower ethical standards of practice.

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