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Developing a Sustainable Renal Transplant Program in Low- and Middle-Income Countries: Outcome, Challenges, and Solutions

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Abstract

Introduction The initiation of a kidney transplant program, in a low- and middle-income country, while striving to maintain excellent outcomes and adhere to high ethical, legal standards, is a formidable task. Herein, we review the outcomes and challenges of a living donor kidney transplant program from its inception to sustainability, in Guyana, South America.

Methods This is a retrospective review of a living donor kidney transplant program instituted in Guyana in 2008. Data included recipient and donor demographics, cause of renal failure, donor–recipient matching and relationship, perioperative complications, timing and cause of death, graft failure, surgical technique, and laterality of organ procured. Patient and donor data were compared by phases and additionally compared to United States Renal Data Base System. Survival outcomes were compared by phases and by Kaplan–Meier curves.

Results To date, 45 kidney transplants have been completed. Phase I (2007–2008) was the initiation of the program, which was comprised of upgrading hospital and operating rooms, obtaining antirejection medications, educating local providers, fostering a relationship with the government, and screening patients and living donors. We also began vascular access and peritoneal dialysis in the country, as well as introduced the companion public health service initiative: the SEVAK program. Phase II (2008–2014) involved completion of 25 living donor kidney transplants, of which there have been 11 confirmed deaths and 10 lost to follow-up. In Phase III (2015–present), 20 transplants have been completed to date, of whom only 1 died and none were lost to follow-up. In the third phase, we also introduced corneal transplantation to Guyana and have performed over 100 transplants.

Conclusion Kidney transplantation can be safely and ethically performed in a low- and middle-income country. We applied lessons learnt from the first two phases to improve follow-up by appointing a local coordinator who goes to patient's homes in remote villages. Currently, there is a stable local team that is performing transplants and following the patients. We believe that our model of public–private partnership can sustain kidney, as well as corneal, transplantation and could be replicated in other countries.

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Abbreviations

PPP	Public–private partnership
LTFU	Lost to follow-up
DM	Diabetes mellitus
HTN	Hypertension
CKD	Chronic kidney disease
PKD	Polycystic kidney disease
RRT	Renal replacement therapy
ESRD	End-stage renal failure
LMIC	Low- and middle-income country
US-NHANES	United States-National Health And Nutrition Examination Survey
GDP	Gross domestic product
HD	Hemodialysis
USRDS	United States Renal Data Base System
PD	Peritoneal dialysis
LDT	Living donor transplant

Introduction

Implementing a kidney transplant program in low- and middle-income countries (LMICs) while striving to maintain excellent outcomes and adhere to ethical legal standards is a formidable task. Herein, we review the outcomes and challenges of a living donor kidney transplant program from its inception through sustainability in Guyana, South America.

Chronic kidney disease (CKD) is a serious health issue affecting people across the world. The main non-infectious causes of kidney disease are hypertension (HTN) and diabetes (DM), both considered primary healthcare issues in most countries. In LMIC, these issues often lack consistent resources for tracking, public education, and treatment. This is especially concerning as HTN and DM, the main causes of CKD, are increasing worldwide [1–3]. It is estimated that 10% of the world population have some degree of CKD, with millions dying each year due to inaccessibility to affordable treatment. Although over 2 million people worldwide receive treatment with dialysis or renal transplant to stay alive, this likely represents only 10% of those who need treatment to survive. The majority of treatment primarily occurs in just five countries: the United States, Japan, Germany, Brazil, and Italy, specifically because of their ease of access to health care as well as their increasing elderly populations.[4]

Indeed, the death burden is high, even in the USA with access to treatment, indefinite dialysis resources, and the opportunity for renal transplant. Comparatively, with limited or no treatment, renal disease and ultimately renal failure lead to a nearly 100% death rate. This was the case in Guyana, where viable treatment was not an option. To make matters worse, there was little public health knowledge and no data tracking system in place to monitor the outcomes of renal disease and its related comorbidities. Extrapolating from the US-NHANES data, it is approximated that 56,160 Guyanese people have CKD 3-5, which is 7.2% of the total population (780,000 people) [5–7].

As compared to the USA, Guyana has limited resources and no nephrologists. At the inception of this transplant program, the only renal replacement therapy (RRT) was hemodialysis (HD), and very limited, with only 3 chairs in the country and no vascular access surgery performed [8]. The Guyana Ministry of Health provided finite funding of $3000–$5000 USD per patient for HD treatment. While the cost of an individual dialysis session has decreased as the number of HD chairs in the country has increased, this still only provides up to approximately 40 dialysis sessions. However, patients in Guyana only go twice per week, for limited hours per session, so they can extend the weeks on dialysis that is paid for by the government. Once the patient has exhausted the government stipend and their family resources, they stop dialysis and typically die within a year.

While HD prolongs the life for months to a year, it still leaves the family drained of resources. Dialysis, as the only mode of RRT, in a country with limited resources, is not a practical nor economical solution for sustaining life and quality of life in the ESRD patient. It has been demonstrated in the USA that the cost of a renal transplant with the patient living approximately 2 years post-transplantation is less expensive versus maintaining a patient on HD for that period of time. In addition, there is a lower mortality rate and better quality of life after receiving a transplant than remaining on HD [7].

Without a long-term solution involving renal transplantation, it can be argued that this expenditure of resources is not efficacious nor sustainable. Kidney transplantation, though costlier upfront, is overall more economical in the long run and provides improved survival outcomes and quality of life [8, 9].

Methods

This is a retrospective review of a living donor kidney transplant program instituted in Guyana in 2008. Data included recipient and donor demographics, cause of ESRD if known, donor–recipient matching and relationship, perioperative complications, timing and cause of death, graft failure, technical aspects of surgery, and laterality of organ procured. Follow-up data were collected on return trips by the US team in conjunction with local coordinators. Patient and donor data were compared by phases and additionally compared to United States Renal Data Base System. Survival outcomes were compared by three phases and examined by Kaplan–Meier curves (GraphPad Prism).

This paper outlines the preliminary steps to building and implementing RRT program in a LMIC. The business aspects and financing were developed as a public–private partnership (PPP) between the US physicians volunteering their services in arrangement with the Guyanese Health Ministry [8, 10]. This model does not rely on direct funding by any US governmental agency [11]. The initial cost was borne by US-based Guyanese Americans and the Subraj Foundation.[1] Later, the Guyana Ministry of Health allowed use of the Georgetown Public Hospital, including generic immunosuppressives, at no charge to the patient. Transportation, lodging, and incidentals for the US team were borne by the Subraj Foundation. The US staff donated their services free of charge and often were required to use vacation time.

All transplants in Guyana are living donor transplants. The left kidney was taken in all cases via an open left flank incision technique. There was no reliable laparoscopic equipment in the country during the development of this program, and thus, no laparoscopic donor nephrectomies were performed. The surgical team consisted of two–three US-based surgeons and a Guyanese surgeon. In 2015, a Guyanese surgeon, after completing fellowship training in abdominal organ transplantation outside the country, began to take over the program. The US team helped with the transition, and several of the transplants were performed with the US and Guyanese teams together.

Donor–recipient pairs were evaluated according to the standard US protocols as defined by UNOS. This transplant program was developed with and maintains adherence to the Declaration of Istanbul on Organ Trafficking and Transplant Tourism [12, 13]. Postoperative follow-up care of the donors and recipients has been carried out by local physicians. The US team has provided consultative management either in person or via telecommunication. Further follow-up evaluations were scheduled in-country within 3–6 months for all patients to be seen in person by the US transplant team.

Results

A total of 45 transplants have been undertaken at the time of this manuscript. The average age of the recipient patients was 38 years, ranging from 17 to 59 years. The recipients included 11 females and 34 males, of which 32 were Indo-Guyanese and 13 were Afro-Guyanese (Table 1). The causes of ESRD include HTN, DM, polycystic kidney disease, nephrotic syndrome, prostatic obstruction, congenital malformation/malfunction and unknown. The majority of the patients' diagnoses were unknown, with the second most common being HTN, followed by DM, then PKD.

We divided the results into three chronological phases (Tables 2, 3, 4, 5). Phase I was the initiation of the program prior to any transplants. Phase II represents renal transplants that were primarily under the direction of the US surgical team. Phase III represents the transplants after program improvements and transition to the Guyana team, in addition to the introduction of the corneal transplant program.

Phase I (2007–2008)

There were no transplantations performed during this time. This represents the initiation of the program, comprised of upgrading facilities, obtaining antirejection medications, teaching local providers, fostering a relationship with the government, and screening patients and potential living donors.

An adjunctive program known as the SEVAK[2] program was also initiated. This is a primary healthcare, public health awareness initiative. A vascular access and peritoneal dialysis (PD) program were both initiated in the country [14].

Phase II (2008–2014)

This phase involved completion of 25 living donor kidney transplants. Of those 25 transplants, there have been 11 confirmed deaths, 10 lost to follow-up (LTFU); the majority were later found to have immigrated from Guyana.

Phase III (2015–present)

In this phase, there were 20 transplants completed, of whom only 1 died and none were LTFU. Dr. K. Persaud, a local transplant surgeon, fellowship trained in Canada, performed 15 transplants during Phase III, and under his direction, the first paired exchange transplant was performed in Guyana in 2018. In the third phase, we also introduced corneal transplantation to Guyana and have performed over 100 transplants [15]. A permanent transplant clinic was initiated with an administrator–coordinator and nursing staff as well as dedicated physicians.

Of the 45 renal transplants in phases II and III, there were a total of 12 confirmed deaths and 10 LTFU. There have been no cases of primary non-function. Of the 12

[1] The George Subraj Family Foundation: https://www.charitynavigator.org/index.cfm?bay=search.profile&ein=472303192.

[2] Sanitation and Health, Education in Village communities through improved Awareness and Knowledge of Prevention/Management of Diseases and Health Promotion.

Table 1 Recipient and donor demographics

Sex	Race		
	Afro-Guyanese	Indo-Guyanese	
Transplant recipients			
Female	5	6	11
Male	8	26	34
	13	32	Totals
Transplant donors			
Female	12	18	30
Male	1	14	15
	13	32	Totals

patients that died (26.7%), 4 were due to sepsis (33.3%), 3 had acute cardiac events (25%), one had a cerebrovascular event (8.3%), and 4 were unknown (33.3%) (Fig. 2). Examining the timeline till death: 4 patients died within 3 months, 0 within 1 year, 1 within 2 years, 1 within 3 years, 1 within 5 years, 4 within 5 years, and 1 within 8 years (Table 2). Of the 10 patients who were LTFU, none were lost prior to 3 years post-transplantation.

Recipient patient survival was first examined by combining the data from phases II and III. These results demonstrate a 90.5% 1-year survival, 79.3% 3-year, and 53.2% 5-year survival. If we include all those LTFU as deceased, to assess the worst possible outcome, the results would be as follows: 90.5% 1-year survival, 55.2% 3-year, and 21.7% 5-year survival (Tables 3, 4). We also examined phases II and III transplant outcomes separately at 1- and 3-year survival. Phase II: 88% 1-year survival and 80% 3-year survival. If LTFU were included, 3-year survival would be 52%. Comparatively, phase III resulted in 95% 1-year and 3-year survival.

Kaplan–Meier curves (Fig. 1) were calculated and compared for phases II and III as well as the aggregate data. The differences in outcomes by phase were found not to be significant ($p = 0.25$) (Table 6). As per Kaplan–Meier calculations, the median survival for phase II was 4.5 years and undefined for phase III.

When examining loss of graft function, we did not include patients who died with a functioning graft. There were 4 confirmed cases of loss of graft function (8.9%). Of the 4 cases, 2 were in patients who also died at 1 and 3 years, both of suspected sepsis in the setting of non-adherence. The two additional grafts with loss of function occurred at 3 and 5.25 years, due to an unknown cause and chronic rejection, respectively. Both of these patients were eventually LTFU.

Donor data

Of the 45 organ donors, there were 30 females and 15 males, of which 32 were Indo-Guyanese and 13 were Afro-Guyanese. The majority were relatives, and there was one known altruistic donor, and one paired exchange [16]. There has been only one confirmed death, approximately 2 years after donating, due to suicide secondary to depression. There has been no other donor-related in-hospital or perioperative or postoperative complications or medical conditions observed by or reported to the US team. There were no wound infections, hernias readmissions, etc., observed by or reported to the US team.

Discussion

Guyana, as compared to the USA, has a number of challenges. It has a lower GDP, a higher birth rate, a shorter life expectancy, a younger median age, and a higher percent of HIV infection [17]. Less than 30% of the population lives in urban areas in Guyana compared to greater than 80% in the USA. Healthcare facilities are primarily in the urban

Table 2 Timeline till Death

Time (years)	# Patient died/year	Phase II	Phase III	Cumulative death total	LTFU per Year	Total LTFU	Total dead + LTFU
0.25	4	3	1	4	0	0	4
1	0	0	0	4	0	0	4
2	1	1	0	5	0	0	5
3	1	1	0	6	7	7	13
4	1	1	0	7	0	7	14
5	4	4	n/a	11	0	7	18
6	0	0	n/a	11	3	10	22
7	0	0	n/a	11			
8	1	1	n/a	12			
	Total			12 (26.7%)		10	22 (48.9%)

Table 3 Survival Outcomes: Overall, Phase II, Phase III

Time (years)	Transplants completed (potential total survival):	Cumulative death total	Total survived	Percent survival	Total LTFU	Cumulative died + LTUF	Percent survival (dead + LTFU)
Combined: Phase II + III							
0.25	45	4	41	91.1%	0	4	91.1%
1	42	4	38	90.5%	4	38	90.5%
3	29	6	23	79.3%	13	10	55.7%
5	23	11	12	52.2%	18	5	21.7%
Phase 2 (2008–2014)							
0.25	25	3	22	88%	0	3	88%
1	25	3	22	88%	3	22	88%
3	25	5	20	80%	12	13	52%
Phase 3 (2015–2018)							
0.25	20	1	19	95%	0	1	95%
1	17	1	16	94%	0	1	94%
3	4	0	4	100%	0	0	100%

Table 4 Kaplan–Meier survival proportions (calculated in Prism by GraphPad)

Years elapsed	Phase II	Phase III	Phases II and III
X	(%)	(%)	(%)
0	100	100	100
0.25	92	95	93.33
1	88	95	91.11
3	80	95	84.97
5	49.23		53.31

centers. Transportation services and roads are underdeveloped, suggesting that, access to health care, from preventative care to complex surgical care, is harder to obtain [18].

In Guyana, the racial/ethnic composition is different from the USA. In Guyana, the population is approximately 40% Indo-Guyanese, 29% Black/Afro-Guyanese, 20% mixed, 10.5% Amerindian, and 0.5% other. This racial/ethnic composition is very relevant when looking at CKD and ESRD. Compared to Caucasians, ESRD prevalence is about 3.5 times greater in African-Americans, 1.5 times greater in Asian-Americans, and 1.4 times greater in Native Americans [19]. Given the higher percentage of Afro- and Indo-Guyanese and the poorer overall health conditions in the country, we would expect the ESRD incidence to be higher than that of the USA.

The primary cause of ESRD in the USA is DM followed by HTN [20]. Comparatively, in Guyana, the most commonly reported cause was HTN and then DM, even though the majority were unknown or not reported to the team. DM and HTN are overall the most common causes of renal disease in both countries as expected, and both countries struggle with the issue of determining a definitive primary cause.

In the USA, survival rates post-transplant and expected remaining lifetime for patients with renal transplant fare considerably better than those on dialysis. The probability of 10-year survival, of patients receiving transplant in 2005, is 78% and 63.5% for living and deceased donors, respectively [21]. In Table 5, the survival rates of the various forms of RRT in the USA are compared to the outcomes of living donor transplant in Guyana at 1-, 3-, and 5-year survival. While the data from the USA are appreciably better than outcomes in Guyana, we believe our outcomes during the initiation and implementation of a new transplant program in a developing country are

Table 5 Renal treatment modality and survival outcomes: comparison of the USA and Guyana living donor transplant

Survival (years)	Living donor transplant (LDT)	Guyana LDT	Deceased donor transplant	Hemodialysis (HD)	Peritoneal dialysis (PD)
1	97.50%	90.50%	93%	78%	89%
3	93%	79.50%	85%	57%	67%
5	87%	52.17	76%	42%	53%
10	78%		63.50%		

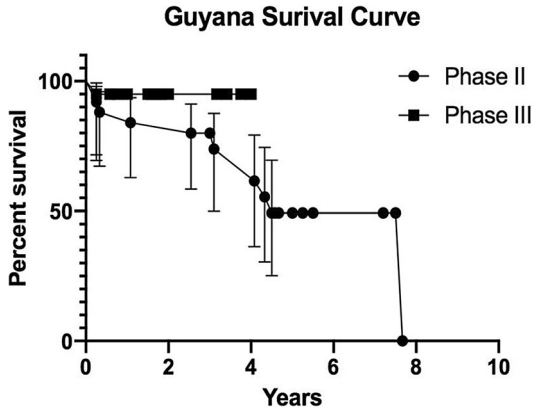

Fig. 1 Kaplan Meier survival curve phase II versus phase III with 95% CI

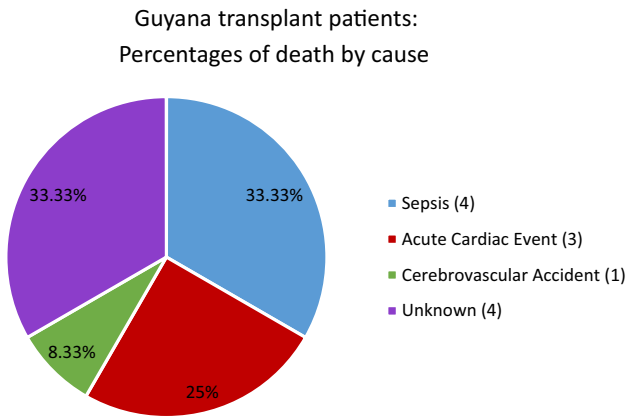

Fig. 2 Cause of death status post-transplant

Table 6 Kaplan–Meier curve comparison data (from Prism by GraphPad)

Comparison of survival curves (phase II and phase III)		
Log-rank (Mantel–Cox) test		
Chi-square	1.604	
df	1	
P value	0.2053	
P value summary	Ns	
Are the survival curves sig different?	No	
Gehan–Breslow–Wilcoxon test		
Chi-square	1.32	
df	1	
P value	0.2505	
P value summary	Ns	
Are the survival curves sig different?	No	
Median survival		
Phase II	4.5	
Phase III	Undefined	
Hazard ratio (Mantel–Haenszel)	A/B	B/A
Ratio (and its reciprocal)	2.81	0.3559
95% CI of ratio	0.5679 to 13.90	0.07193 to 1.761
Hazard ratio (log-rank)	A/B	B/A
Ratio (and its reciprocal)	2.972	0.3365
95% CI of ratio	0.7457 to 11.84	0.08443 to 1.341

acceptable. The results continue to improve with sustainability in phase III.

It is important to highlight several outcomes. Comparing survival from receiving a renal transplant in Guyana vs living on HD in the USA demonstrates superior outcome receiving a transplant in Guyana. The aggregated 1-, 3-, and 5-year survival for all transplants completed to date in Guyana, 90.5%, 78.3%, and 52.2%, respectively. When compared to HD in the USA at 1-, 3-, and 5-year survival, which is 78%, 57%, and 42%, respectively, transplant in Guyana has superior outcomes. We have not observed long-term, greater than 1 year, survival on HD. We expect the 1-year survival to be essentially nil, given that there is a finite funding for HD. Additionally, there are an insufficient number of chairs, even with a continued increase, with 40 chairs in 2017 and the public hospital offering free, albeit limited HD. Patients do not have the chance to live 3–5 years on HD in Guyana [22]. Additionally, prior to this program there was no PD program or vascular access available within the country. Increased use of vascular access surgery will presumably decrease the catheter-related infections; however, we did not collect these data.

Another important point to note is the improved survival outcomes from phase II (2008–2014) to phase III (2015–present) in the 1- and 3-year survival. We believe this increase in patient survival in phase III is in part due to the introduction of designated personnel for follow-up and dedicated in-country team. In Guyana, the causes of recipient mortality were similar to the USA, with the three major categories being unknown (33%), sepsis (33%), and cardiovascular (25%) (F). There was a higher prevalence of mortality from sepsis in Guyana than the USA (33% vs 17%). We speculate this may be due to limited access to clean water and indoor toilet facilities. It is also possible that some of the unknown deaths are due to sudden cardiac death secondary to arrhythmias, as is suspected to represent a larger percent of deaths in the USA [8].

We believe that our humanitarian mission has accomplished a number of goals. It introduced vascular access, PD, contributed to the growth of HD access and introduced

Table 7 Key elements for a successful RRT in low–middle-income countries

1	Impact of the program overall
2	Resource identification
	(a) Level and complexity of resources needed
	(b) Personnel
	(c) Equipment
	(d) Infrastructure
	(e) Durability of the resources
3	Aligning the goals of the program with the needs and the goals of the country
	(a) Political outreach and education
	(b) Public education
4	Financial structures and funding sources
	(a) Accounting—overall costs through development to sustainability
	(b) Accountability
5	Sustainability of the initiative
	(a) Political education
	(b) Legislative changes
	(c) Outreach/PR
	(d) Education of local personnel
	(e) In-country personnel with primary responsibility of the program
6	QAPI = Quality assurance performance improvement

kidney transplant, thus providing access to all aspects of RRT in Guyana. As a result, we have witnessed increased life expectancy and improved quality of life for patients as well as their families. This program has increased awareness of primary health issues, such as BP control and glucose monitoring, by aligning with government primary health initiatives, which are being carried out through the SEVAK program [19, 23–26].

A high-impact, low-cost, low-resource program is sustainable in a LMIC by adopting the elements that are outlined in Table 7. Laying the ground work is important. Surgical initiatives are more complicated given the need for sterile facilities, operating and recovery rooms as well as trained personnel. Specialized surgical procedures are even more complicated, as the initiative depends on the availability of the specialist to come to the country in question. In addition to this infrastructure, initiatives that are looking for a sustainable long-term impact will need host country government and health administration support and political buy-in. This vital piece includes educational sessions and aligning the program with the ministry of health goals. We demonstrated that a complex surgical program such as living donor renal transplantation does align with public health and ultimately influences primary healthcare outcomes. In working with the Ministry of Health, we supported their preventative health initiatives, which, for example, we facilitated through the free kidney clinic, local media promotion of primary healthcare initiatives, corneal transplantation and through introduction of the SEVAK program [25–27]. Thus, we were able to increase public education and awareness of the importance of early intervention and treatment in the diseases that lead to CKD and ESRD.

Recognizing the importance of a sustainable financial structure, we have developed a PPP [8]. We have kept the cost of each kidney transplant under $15,000 USD. The yearly costs of immunosuppression and laboratory evaluation including approximately 28 follow-up office visits are estimated to be $2000 USD. The Guyanese government has been instrumental in supporting transplantation costs as well as funding long-term follow-up costs.

We recognize the limitations in our data, due to limited patient volume, length of time, and inconsistent follow-up [28]. This is in part due to physicians, healthcare workers, and facilities changing over time. Having a more stable team in place with set communication parameters allows for increased reliability and sustainability. A possible solution to timely follow-up in this country might require home outreach visits, as many of these patients have difficulty reaching the healthcare facilities [29]. Finally, we believe the core of this model to be adaptable to many other countries facing similar health challenges, serving as a way to bridge the disparity gap and be of major benefit to upgrading infrastructure of healthcare delivery.

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