ORIGINAL ARTICLE

Ten-year Outcomes of Kidney Transplants at the Singapore General Hospital

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ABSTRACT

Renal transplantation is the treatment of choice for kidney failure. This study analyses the outcomes of kidney transplant recipients whose transplant was performed at the Singapore General Hospital from January 2000 to 31 December 2010, and who have had at least a year of follow-up in the hospital. Patient demographics, recipient and donor characteristics, graft and patient outcomes were extracted from patients' electronic and hard copy medical records. Graft and patient survival were calculated by Kaplan-Meier analysis until return to dialysis or patient death.

There are 332 deceased donor (DD) and 118 live donor (LD) kidney transplants included in this study. Majority of our transplant recipients were Chinese males, and the most common etiology of renal failure was chronic glomerulonephritis. DD recipients were significantly older than LD recipients (45.3+8.2 years vs. 36.9+11.7 years, respectively, P <0.001), and also had a significantly longer duration of dialysis (8.6+2.6 years vs. 2.3+3.5 years, respectively, P <0.001). Majority were on haemodialysis prior to transplantation. DD were significantly older than LD (45.7+8.2 years vs. 37.1+11.8 years, respectively, P <0.001); 73.2% of our DD were standard criteria donors. Graft survival at 5 years was 80.8% and 96.5%, and 65.9% and 79.4% at 10 years for DD and LD transplants, respectively. Patient survival at 5 years was 91.5% and 82.7%, and 99.1% and 84.7% at 10 years for DD and LD transplants, respectively. LD recipients had improved graft and patient survival compared to DD recipients, reinforcing LD kidney transplantation as the treatment of choice for patients with end-stage renal failure.

Keywords: Deceased donor, Kidney, Live donor, Outcomes, Transplant

INTRODUCTION

Renal transplantation (RTx) has been an option for the treatment of end-stage renal failure (ESRF) in Singapore since 1970 when the first cadaveric RTx was performed. Since this historical transplant, the kidney transplant programme at the Singapore General Hospital (SGH) has been witness to many other landmark transplants, such as the first living kidney donor transplant in 1976, the first laparoscopic donor nephrectomy in 2004 and the first dual kidney transplant in December 2009; and has had over 850 recipients and over 150 living kidney donors under its follow-up since the inception of the programme. Our transplant programme has also been at the frontiers of RTx by performing complex transplants such as positive B-cell crossmatch deceased donor kidney transplantation since 2007, a living kidney donor transplant from a 75-year-old mother, the oldest living kidney donor in Singapore in July 2009, and ABO-incompatible living kidney donor transplant since November 2009.

Over the last 10 years, we have witnessed marked improvements in graft survival due to pharmacological and surgical advances. The pharmacological advances include not only new immunosuppressants, but also more effective and stronger antiviral, antibacterial and antifungal agents, which have contributed to improved patient survival. Apart from this, there has also been an increase in the number of patients who have received a deceased donor (DD) RTx in the 2000s, compared to the 1980s, following amendments to the Human Organ Transplant Act (HOTA) such as inclusion of all causes of death compared

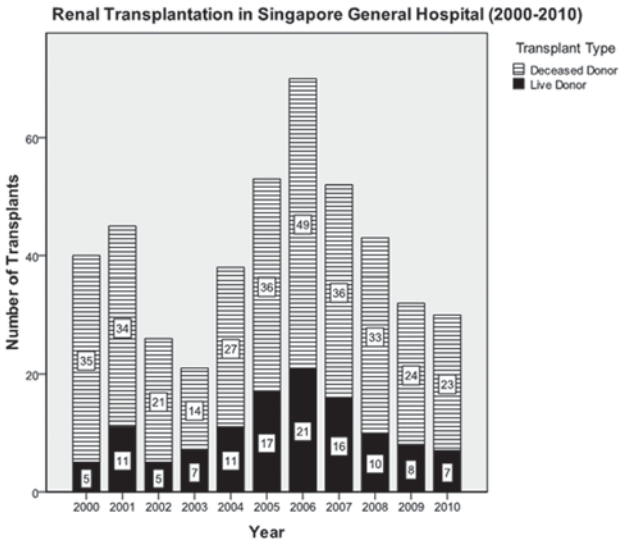

Fig. 1. Deceased donor and living donor kidney transplants at Singapore General Hospital from 2000-2010

to accidental deaths only in 2004, inclusion of Muslims in 2008 and removal of the upper age limit for donors in 2009.

This article summarises the short- and long-term outcomes of transplantation for patients who have been transplanted between 2000 and 2010 with at least one-year of follow-up data, and are currently on follow-up at the SGH, one of the two public sector hospitals with transplant programmes in Singapore.

PATIENTS AND METHODS

Between 2000 and December 31 2010, 118 live donor (LD) RTx and 332 DD RTx have been performed in our centre.

During this same period, there were 161 patients who had undergone RTx in overseas centres. Of these patients, 137 patients had undergone RTx in China, 11 patients had undergone RTx in India and 13 patients had undergone RTx in other overseas centres. Another 13 patients had their kidney transplant surgery performed at private hospitals in Singapore. Donor characteristics and initial transplant immunosuppression were largely unknown for these transplants. All of these patients were excluded from the current analysis.

Information regarding recipient demographics, graft and patient status such as graft loss, patient death, or loss to follow-up and causes of graft loss and patient death were obtained from a retrospective review of the patients' electronic and hard copy medical records. Donor characteristics were obtained for both DD and LD transplant recipients. The mean cold ischaemic time was determined from 397 patients in the study population, as 53 patients had this information missing from their hard copy medical records and electronic records were only available after 2004 in our centre.

Causes of graft failure were classified based on allograft biopsy and clinical course. Rejection (REJ) as a cause of graft loss was diagnosed in those who had documented biopsy evidence of acute or chronic rejection. Chronic allograft nephropathy (CAN) was diagnosed based on graft damage identified on biopsy, characterised by interstitial fibrosis and tubular atrophy (IFTA) and representing the response to graft injury. Patients with calcineurin inhibitor nephrotoxicity and progressive allograft dysfunction without a current biopsy were also included in this category after excluding other known causes of graft dysfunction.

Patients who passed away with a functioning graft, defined as serum creatinine <250 mmol/L, were classified as death with a functioning graft. For the purposes of this study, they were included as a cause of graft failure and as deaths in the analyses for graft and patient survival, respectively. Patients lost to follow-up, such as those returning to their home country or transferring to another hospital, were censored for graft and patient survival analyses from the date of last visit. All patients were

Table 1. Recipient, Donor and Transplant Characteristics of Deceased Donor (DD) and Living Donor (LD) Kidney Transplants.

	Transplant Type	
	DD	**LD**
Recipient Characteristics		
Age[a] (years)	45.7 ± 8.2	37.1 ± 11.8[b]
Males, n (%)	169 (50.9)	60 (50.8)
Race, n (%)		
: Chinese	277 (83.4)	71 (60.2)
: Malay	41 (12.4)	41 (34.8)
: Indian	21 (3.6)	3 (2.5)
: Others	2 (0.6)	3 (2.5)
Duration of dialysis[a] (years)	8.6 ± 2.9	2.6 ± 3.7[c]
Etiology of End-Stage Renal Failure, n (%)		
: Chronic glomerulonephritis	233 (70.2)	82 (69.5)
: Diabetic nephropathy	4 (1.2)	4 (3.4)
: Hypertensive nephrosclerosis	4 (1.2)	9 (7.6)
: Lupus nephritis	8 (2.4)	7 (5.9)
: Autosomal Dominant Polycystic Kidney Disease	14 (4.2)	5 (4.2)
: Reflux nephropathy and congenital anomalies	9 (2.7)	6 (5.1)
: Others	60 (18.1)	5 (4.2)
Cold ischaemic time (hrs)[f]	12.5 ± 5.5	1.32 ± 3.8
Donor Characteristics		
Age[a] (years)	44.7 ± 11.7	42.3 ± 11.0[d]
Males, n (%)	210 (63.3)	48 (40.7)[e]
Donor relationship		
: Parent		26 (22.0)
: Sibling		44 (37.3)
: Spouse		32 (27.1)
: Offspring		6 (5.1)
: Others		10 (8.5)
Donor cause of death (%)		
: Cerebrovascular Accident	225 (67.8)	
: Head Trauma	54 (16.3)	
: Judicial Death	44 (13.3)	
: Others	9 (2.7)	
Deceased Donor Type		
: SCD	241 (72.6)	
: ECD	47 (14.2)	
: DCD	44 (13.3)	
Immune risk		
: Retransplant	6 (1.8)	1 (0.8)
: ABO incompatible	0 (0)	1 (0.8)

[a]Values reported as mean ± standard deviation
[b,c,e] P <0.001
[d] P=0.05
[f]CIT calculated for 296 DD recipients & 99 LD recipients as 53 patients had missing data

followed-up until graft loss, patient death, loss to follow-up or until December 31, 2011.

STATISTICAL METHODS

Statistical analyses were performed using STATA/MP v.10.0 (StataCorp, College Station, TX, USA) as well as SPSS statistical software. Unadjusted graft survival rates were estimated using Kaplan-Meier analysis, and statistical comparisons of survival curves were done by the log-rank test. Categorical variables were compared by means of the chi-square test, and continuous variables were compared via the Student's *t* test, with a two-tailed *P* value of <0.05 considered as significant.

RESULTS

During the 10-year period from 2000-2010, 118 LD and 332 DD transplants had been performed in our centre (Fig. 1). Following various amendments to HOTA, the number of DD transplants rose to a peak in 2006. LD transplant numbers also rose since 2002 to a peak in 2006, but has been gradually declining since then, though the numbers remain slightly higher than the early 2000s. The number of DD transplants each year has been falling since, which could partly be due to improved road safety.

The demographics and clinical characteristics of our kidney transplant recipients are shown in Table 1.

DD recipients were significantly older with a mean age of 45.3 ± 8.2 years compared to LD recipients, whose mean age was 36.9 ± 11.7 years (P <0.001). Dialysis patients without a suitable living donor had to wait much longer for a transplant compared to those with a LD; this corresponded to their significantly longer duration of dialysis compared to LD recipients (8.6 ± 2.6 years vs. 2.3 ± 3.5 years, respectively, P <0.001). Unfortunately due to the increasing number of patients reaching ESRF and the scarce resources, the median waiting time for a DD kidney transplant for patients on the National Transplant Registry (NTR) in Singapore was 9.4 years at the end of 2008[1,2].

There was gender equality among both DD and LD recipients and the racial distribution in both groups were broadly similar to that of the Singapore general population, with the exception of an increased proportion of Malay patients who have received a LD transplant.

The etiology of ESRF was predominantly chronic glomerulonephritis (CGN) in both groups. There was a higher proportion of patients with ESRF due to lupus nephritis, reflux nephropathy and other congenital anomalies who had received a LD transplant. Interestingly, the majority of their transplants were from a parent, that is four out of the seven patients in the former group, and five out of six in the latter group received a kidney from a parent. A possible reason could be that these patients tended to develop ESRF at a younger age and not surprisingly, their parents were willing to step forward as potential donors to save them from a lifetime of dialysis dependence.

Slightly more than a third of all LD transplants (35%) were pre-emptive transplants, that is, RTx was performed before the patient required dialysis. The predominant modality of renal replacement therapy in both groups was haemodialysis prior to RTx (95.5% vs. 84.7% in DD and LD recipients, respectively).

Deceased donors (DD) were predominantly male (63.3%) with a mean age of 44.7 ± 11.7 years. Their leading cause of death was cerebrovascular disease. The majority (73.2%) of DD were standard criteria donors (SCD), 14.2% were expanded criteria donors (ECD), and the remaining 12.7% were non-heart beating donors, that is donation after cardiac death (DCD). The definition of SCD and ECD is according to that of the Organ Procurement and Transplantation Network/United Network of Organ Sharing (OPTN/UNOS)[3], that is an ECD refers to any brain dead donor over the age of 60 years or a kidney donated for transplantation from a donor over the age of 50 years with two of the following: a history of hypertension, most recent serum creatinine ≥1.5 mg/dL, or death resulting from a cerebral vascular accident (stroke). DCD refers to a donor whose heart has irreversibly stopped beating, while SCD refers to a donor who has suffered brain death (as opposed to cardiac death) and who is not an ECD.

There were significantly more female living donors (59.3%), and the majority were biogically related (64.4%), that is the donors were either a parent, a sibling or a child (22.0%, 37.3% and 5.1%, respectively). Almost a third of all LD recipients (27.1%) received a kidney from their spouse, that is emotionally related donors.

For their immunosuppression, the majority received a calcineurin inhibitor, that is Cyclosporine A or Tacrolimus, mycophenolate analogs and steroids. Since 2009, the majority of patients transplanted in our centre have also received induction immunosuppression, either in the form of an interleukin-2 receptor antagonist or a lymphocyte depleting agent.

Graft and patient outcomes for DD transplants and LD transplants are shown in Table 2 (see overleaf). Patient survival was generally better than graft survival (Table 2), unsurprising as patients can return to dialysis following graft failure. The predominant cause of graft loss in our patient population was death with a functioning graft,

Table 2. Graft and Patient Outcomes of Deceased Donor (DD) and Living Donor (LD) Kidney Transplants.

	Transplant Type	
	DD	**LD**
Graft Outcomes		
Graft survival (%)		
: 1 year	89.8	98.2
: 3years	85.9	98.2
: 5 years	80.8	96.5
: 10 years	65.9	79.4
Number of Graft Losses	79 out of 332 (23.8)	7 out of 118 (5.9)
Causes of Graft Loss (%)		
: Primary non-function / Thrombosis	11 (13.9)	1 (14.3)
: Rejection (REJ)	18 (22.8)	0 (0)
: Chronic allograft nephropathy (CAN) / calcineurin inhibitor nephrotoxicity / Recurrence of original disease	13 (16.5)	3 (42.9)
: Death with functioning graft	27 (34.2)	3 (42.9)
: Others	10 (12.7)	0 (0)
Patient Outcomes		
Patient survival (%)		
: 1 year	96.7	99.1
: 3 years	94.8	99.1
: 5 years	91.5	99.1
: 10 years	82.7	84.7
Number of Patient Deaths	37 out of 332 (11.1)	4 out of 118 (3.4)
Causes of Patient Death (%)		
: Infection	15 (40.5)	2 (50.0)
: Malignancy	2 (5.4)	1 (25.0)
: Cardiovascular / Cerebrovascular	12 (32.4)	1 (25.0)
: Others	8 (21.6)	0 (0)
Causes of Graft loss were analysed as a proportion of all graft losses. 3 DD patients and 37 LD patients who had gone back to home country, transferred to another hospital or lost to follow-up were censored for analyses of graft loss and patient death.		

consistent with previous studies, followed by REJ and CAN for DD recipients. CAN and death with a functioning graft were equally common among LD recipients. The leading cause of patient death was death related to infections, followed by cardiovascular or cerebrovascular causes of death.

Recipients of LD kidneys had better graft and patient survival rates than DD kidney recipients (Figs. 2 and 3; see overleaf). This could be due to the significantly shorter cold ischaemic time in LD kidney recipients (1.3 $\pm$ 3.8 hours vs. 12.5 $\pm$ 5.5 hours in LD and DD recipients, respectively, P <0.001), among other factors (Table 1). This reinforces the importance of minimising the cold ischaemic time following allograft retrieval as it is an important factor in initiating the cascade of events resulting in ischaemic reperfusion injury. Importantly, graft survival rates at 1, 3, 5 and 10 years in our patient population are 89.8%, 85.9%, 80.8% and 65.9%, respectively for DD and 98.2%, 98,2%, 96.5% and 79.4%, respectively for LD kidney transplants, greatly exceeding those reported in the United States of America and Europe[3,4], a finding consistent with previous reports from our institution and other Asian centres[5,6].

DISCUSSION

The overall 10-year graft and patient survival rates in our centre are 69.4% and 83.8%, respectively. The advent of more potent immunosuppressants, newer and better antibiotics and antifungals over the years, have all contributed to improved survival rates[5]. The results of our single-centre study are

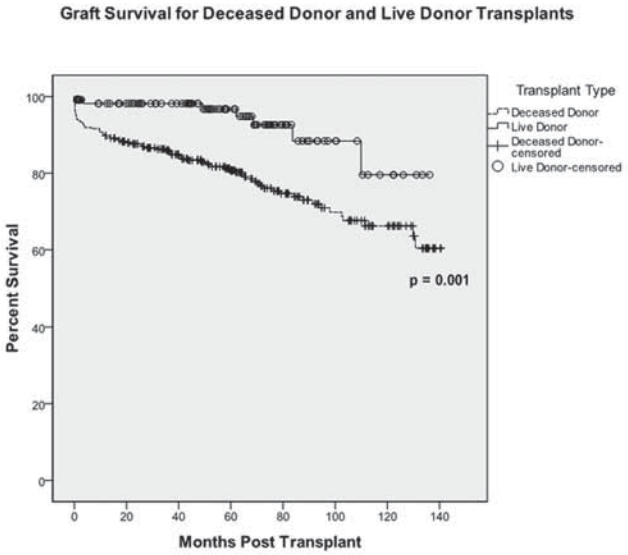

Fig. 2. Graft survival for deceased donor and live donor transplants

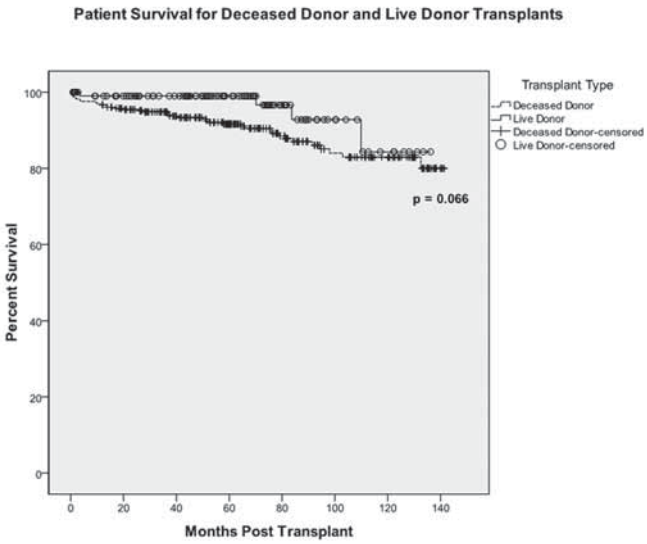

Fig. 3. Patient survival for deceased donor and live donor transplants

also better than those reported from multi-centre registries. Possible reasons for the longer DD kidney transplant survival include the strict eligibility criteria which dialysis patients in Singapore have to meet before being placed on the National Transplant Registry (NTR), including the absence of clinically overt cardiovascular and cerebrovascular disease. Diabetics who are on the NTR have to first undergo a coronary angiogram to exclude significant coronary artery disease, resulting in a low number of diabetics who actually receive a DD transplant. Furthermore, prior to 2009, only patients below the age of 60 were allowed to be on the NTR; younger patients without cardiovascular or cerebrovascular disease are likely to have longer patient survivals.

The excellent overall graft survival rate has been helped by government subsidies for immunosuppression, which have contributed to increased patient compliance with medications. Unlike overseas centres, all kidney transplant recipients in Singapore have lifelong follow-up in a tertiary hospital with a nephrologist, which could be another factor contributing to good long-term outcomes[5]. Importantly, our results have also confirmed that LD kidney transplants have better short- and long-term survival rates compared to DD kidney transplants. This is why the renal replacement therapy of choice for all patients with ESRF in general should be a LD kidney transplant (unless there are medical contraindications), as it affords patients improved survival rates, in addition to a life free from the constraints of dialysis.

Analyses of the OPTN/UNOS database have shown significant improvement in short-term graft survival from the mid-1970s to the 21st century; long-term graft survival however, has not seen similar improvements[7]. This is despite the advent of new pharmacological agents and improvements in surgical techniques. Terasaki et al have demonstrated that anti-HLA antibodies, especially those that develop post-transplant, are an important cause of decreased long-term graft survival[8]. For financial reasons, our patients do not routinely undergo screening for such antibodies. Moving forward, we could start testing those patients with deteriorating graft function for anti-HLA antibodies, in addition to other routine tests, with the intent of commencing antibody-neutralisation or removal therapies, for example intravenous immunoglobulin infusions, plasmapheresis, or Bortezomib, should these antibodies be present. This could lead to an improvement in long-term graft survival rates. Research is also ongoing for newer, more potent immunosuppressants with less side-effects, including an improved cardiovascular risk factor profile. It is greatly anticipated that such drugs, if made available, would allow for immunosuppression with less side-effects and further improve long-term graft survival.

The increasing shortage of organs available for renal transplantation has led to the consideration of alternative national strategies for increasing the donor pool. Since the early 1990s, the use of marginal donors and ECD have resulted in increased numbers of transplanted patients,

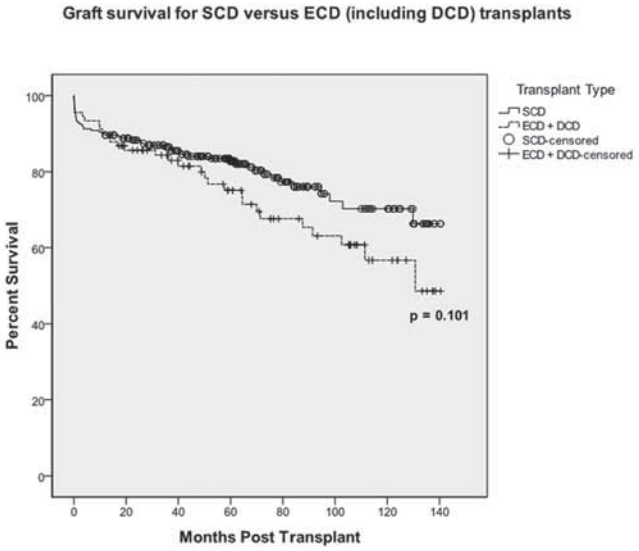

Fig. 4. Graft survival of SCD versus ECD (including DCD) transplants

providing a survival advantage to these patients as compared with patients maintained on dialysis, with a gain in life expectancy ranging from 3 to 9 years[9]. Our data showed inferior graft survival for ECD kidneys compared to SCD kidneys (Fig. 4), which is consistent with larger studies and analyses from other transplant registries. Moving forward, age-matching of donors and recipients should be considered; alternatively, ECD kidneys could be allocated to older recipients whose metabolic demands are lower[10].

Infection or sepsis was the leading cause of death in both DD and LD recipients as compared to cardiovascular or cerebrovascular causes in other transplant registries. This could be partly due to the relatively young study population, and partly due to the strict medical criteria which DD recipients have to meet before RTx. Though CGN was the predominant cause of ESRF in our transplant population, the diagnosis of recurrent glomerulonephritis (GN) was not common, as this requires histologic confirmation of the same disease involving both the native and transplanted kidneys. As a histologic diagnosis is often not obtained for patients with ESRF, coupled with the tendency of clinicians to make a clinical diagnosis of CAN without biopsy in patients with declining graft function and proteinuria, the true incidence of disease recurrence is under-represented here. This is in contrast to registry data showing GN recurrence to be one of the top causes of graft failure[3,4].

In summary, this study has demonstrated the excellent short- and long-term graft and patient survival rates of kidney transplant recipients in our centre. Some of the factors contributing to this have been discussed. The most pressing task at hand would be to increase the number of LD kidney transplants, for example through public education, as they afford the best graft and patient survival rates for ESRF patients. Following the more frequent use of induction immunosuppression in our DD transplant recipients since 2009, it would be interesting to monitor long-term graft survival rates for these patients.

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