Original Article

Nineteen-Year Experience of Paediatric Renal Transplantation in Singapore

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Abstract

Introduction: Renal transplantation is the treatment of choice for children with end-stage renal failure (ESRF). The paediatric renal transplant programme in Singapore was initiated in 1989. This study aimed to examine our outcomes over the 19-year period from 1989 to 2007. Materials and Methods: A total of 38 renal transplants were performed at our centre. Another 4 patients with overseas transplants who returned within 3 weeks post-transplant were included. The proportion of living donor (LD) transplants was 61.9%. Structural abnormalities and glomerulopathies were the most common aetiologies comprising 33% each. Median age at transplant was 13.9 years and median waiting time was 2.2 years. LD transplant recipients were younger and had a shorter waiting time than deceased donor (DD) recipients. Results: Overall patient survival rates were 95%, 92%, 86% and 86% at 1, 5, 10 and 15 years, respectively. There were 4 deaths, of which 3 were due to infections. Graft survival rates at 1, 5, 10 and 15 years for LD and DD transplants were 100%, 89.5%, 67.3%, 67.3% and 80.8%, 56.5%, 42.2%, 28.3% respectively, and were significantly higher in LD transplants. The main cause of graft loss was rejection following non-adherence. Multivariate analysis showed male gender, late acute rejections and acute tubular necrosis as predictors of graft failure. There was a high incidence of early bacterial infections (42.9%) and cytomegalovirus disease (16.7%). Conclusion: Our graft survival rates for LD transplants were comparable to North American rates, although our DD transplant rates were slightly worse, probably a reflection of the prevailing transplant policies.

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Key words: Deceased donor, Living donor, Paediatric transplantation

Introduction

Renal transplantation is the treatment of choice for children with end-stage renal disease (ESRD)[1] as it results not only in better survival rates but also better quality of life compared to dialysis.

In Singapore, the Paediatric Renal Replacement Programme was set up at the University Children's Medical Institute (UCMI) in 1988 and the first paediatric renal transplantation in Singapore was performed in February 1989 in a child of 3.4 years of age. Today, the UCMI is the only centre that performs paediatric renal transplantation in Singapore. When the Programme was first set up, we faced the initial problems of constrained resources, parental apprehension, lack of government support, limited expertise and lack of priority for paediatric patients in the deceased donor (DD) waiting list. Since then, our Programme has expanded not only in terms of patients, but also in resources and expertise. Awareness of paediatric chronic kidney disease has also increased among our patients, and in our healthcare community, leading to better allocation priorities of DD kidneys for paediatric patients. Our current challenges now stem from the maintenance of a programme in a small country with a relatively small patient pool and limited financial resources for many families.

The aim of this study was to examine the outcomes of our paediatric renal transplant programme over the 19-year period from 1989 to 2007.

Patients and Methods

Medical records of patients who had their renal

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transplantation in the UCMI during the period of 1989 to 2007 were reviewed. Data were obtained from a database approved by the Institutional Review Board.

Information on age, gender, ethnic groups, native kidney disease, pre-transplant dialysis time, acute rejection episodes, adherence, serum creatinine, causes of graft failure and death was collected. Graft failure was defined as a return to dialysis or death with a functioning graft. Acute tubular necrosis (ATN) was defined as serum creatinine of more than 150 μmol/L by the end of the first week after transplant. Acute rejection episodes were defined as a rise in serum creatinine of at least 20% accompanied by anti-rejection therapy. Early acute rejections were defined as episodes occurring within 6 months after transplantation, while late acute rejection episodes were those that occurred after 6 months. Acute rejection episodes were treated with intravenous bolus doses of methylprednisolone for 3 consecutive days. For the purpose of this study, chronic rejection was defined as the progressive loss of renal function expressed as a slow increase in serum creatinine excluding other causes. Glomerular filtration rates (GFRs) were calculated using the Schwartz formula.[2] Adherence was evaluated based on trends in cyclosporine or tacrolimus levels, attendance at clinic visits or scheduled blood tests, and individual interviews.

From 1989 to 1997, patients received induction therapy with either OKT3 or anti-thymocyte globulin, followed by triple therapy with steroids, azathioprine and cyclosporine. After 1997, patients received induction therapy with anti-interleukin-2 receptor (IL-2R) antibodies, either Basiliximab or Dacluzimab, and thereafter steroids, mycophenolate and calcineurin inhibitors. Cyclosporine was initially used, before being replaced by tacrolimus in 2004. To study the effect of the different treatment strategies and their impact on graft survival, we divided the period of 1989 to 2007 into 2 immunosuppressive eras: 1989 to 1997 and 1998 to 2007.

Statistical Analysis

Statistical analysis was performed using SPSS 16.0 for Windows (Stata Corp, College Station, Texas, USA). Continuous variables were described by median and range, and categorical data by frequencies and percentages. Demographic, clinical and laboratory characteristics were compared between groups. The chi-square or Fisher's exact tests were used to compare categorical variables, while the Mann-Whitney test was used to compare continuous variables. Crude patient and graft survival rates were calculated using Kaplan-Meier survival analysis and computed with follow-up times of 1, 5, 10 and 15 years. The log-rank test was used to determine differences in survival between different groups.

Multivariate Cox proportional hazard model was used to estimate hazard ratios and to identify independent predictors of graft loss. The model was fitted and adjusted for gender, race, waiting time, recipient age at time of transplant, type of transplant (living versus DD), immunosuppression era, ATN, adherence, cytomegalovirus (CMV) disease, early and late acute rejection, and chronic rejection episodes. $P < 0.05$ (two-sided) was considered statistically significant.

Results

Patient Characteristics

During the years of 1989 to 2007, 38 renal transplants were performed at the UCMI. Of these, 37 were primary transplants and 1 was a second transplant after the first transplant performed overseas failed. Another 4 patients who received their DD transplants from overseas centres and returned to the UCMI within the first 3 weeks post-transplant for continuation of management, were included, giving an overall total of 42 patients. No multiple organ or pre-emptive transplants were performed during this period. Of these 42 patients, 1 patient was lost to follow-up 14.2 years after the transplant, and 2 patients was followed up in overseas centres at 8.2 and 16.0 years after their transplants. The total follow-up rate in our study was therefore 92.9%.

The primary diseases leading to end stage renal failure (ESRF) are shown in Table 1. Structural abnormalities, especially renal dysplasia and/or hypoplasia, and glomerulopathies, in particular focal segmental glomerulosclerosis (FSGS), were the most common aetiologies, comprising 33% each.

In the first 10 years, 14 children were transplanted in our centre. Of these, 10 (71.4%) were living donor (LD) transplants. The first DD kidney transplant was performed at our centre in December 1994. Overall, DD transplants comprised 38.1%. Excluding the 4 overseas DD transplants, the proportion of DD transplants was 31.6% of the transplants performed in UCMI. LD transplants comprised 61.9% overall, of which the majority were from parents (84.7%). The rest were from siblings, aunts or cousins. The median age of the recipients at transplantation was 13.9 years (range, 3.4 to 27.1). As shown in Table 2, LD transplant recipients were significantly younger (median 10.1 years) than those who had a DD (median, 12.9 years) ($P = 0.019$), and they also had a shorter waiting time (median, 1.5 years) compared to those who received a DD allograft (median, 4.9 years) ($P < 0.001$) (Table 2). All our patients less than 6 years of age received a LD transplant. More than half of our transplants were performed in adolescents between 11 and 21 years of age. Almost one-fifth of our transplants were performed in young adults greater than 21 years old, all of whom had entered the Paediatric Renal Replacement Programme before the age of 18 years.

Table 1. Primary Renal Diseases in Transplanted Children (n = 42)

Renal diseases	n
Structural abnormalities (%)	**14 (33%)**
Neurogenic bladder	1
Obstructive uropathy	1
Dysplasia/hypoplasia	7
Reflux nephropathy	5
Glomerulopathies (%)	**14 (33%)**
FSGS	6
Other primary glomerulonephritis	6
Lupus nephritis	2
Hereditary diseases (%)	**6 (14%)**
Nephronophthisis	3
Polycystic kidney disease	1
Familial membranous nephropathy	2
Acquired diseases (%)	**6 (14%)**
Acute cortical necrosis	1
Bilateral renal vein thrombosis	1
Hemolytic uremic syndrome	2
Chronic tubulo interstitial nephritis	1
IgA nephropathy	1
Unknown (%)	**2 (5%)**

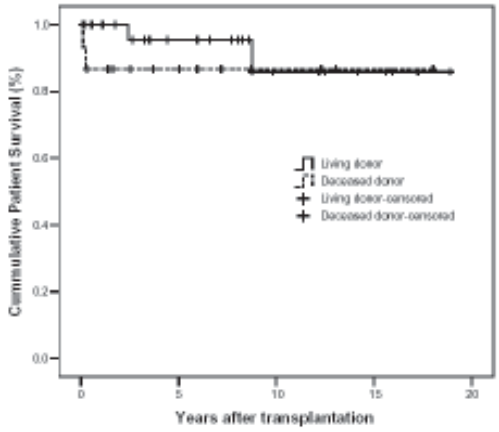

Fig. 1. Cumulative patient survival by donor type.

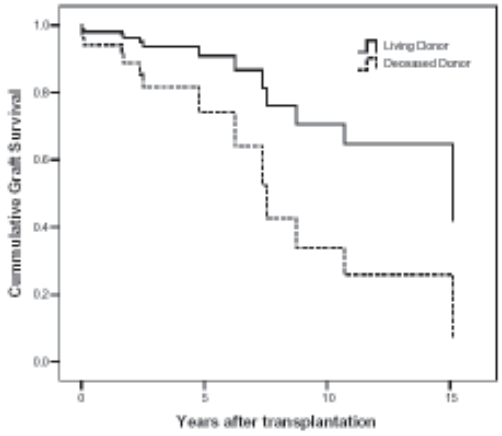

Fig. 2. Cumulative graft survival by donor type, adjusted for gender, race, waiting time, recipient age at time of transplant, immunosuppression era, and adherence.

The 4 overseas transplants were performed in China and were all from DDs. The cold ischaemic times for these transplants were not known. For the local DD transplants, the median cold ischaemic time was 11.5 hours (range, 0.42 to 25 hours). In relation to this, 1 (3.8%) LD transplant recipient and 6 (37.5%) DD transplant recipients had ATN, of whom 3 (including one LD recipient) required dialysis.

Patient Survival

By the end of the 19-year study period, 38 (90.5%) patients were alive with a median age of 21.5 years (range, 6.0 to 35.0 years). Overall patient cumulative actuarial survival rates were 95%, 92%, 86% and 86% at 1, 5, 10 and 15 years, respectively (Fig. 1). Patient survival was not significantly different between LD/DD transplants (P = 0.22) nor between the 2 immunosuppressive eras (P = 0.67) though there was a trend towards better survival in LD transplants and in the later immunosuppressive era of induction therapy with IL-2 receptor antagonists. During the study period, there were 4 deaths (9.5%), including 1 due to a road traffic accident. One patient died due to severe cytomegalovirus (CMV) infection at 2.4 years after transplant, and another due to acute *Escherichia coli* gastroenteritis-associated thrombotic thrombocytopaenic purpura at 95 days after transplant. The last patient died at 40 days post-transplant of nosocomial sepsis after a stormy 1-month stay in the critical care unit for haemolytic uremic syndrome secondary to donor-transmitted dengue infection.

Graft Survival

Overall cumulative actuarial graft survival rates during the study period were 92.8%, 77.5%, 58.7% and 52.2% at 1, 5, 10 and 15 years, respectively. Actuarial graft survival rates for LD transplants were 100%, 89.5%, 67.3% and 67.3% at 1, 5, 10 and 15 years post-transplant, respectively. Corresponding rates for DD transplants were 80.8%, 56.5%, 42.2% and 28.3%, respectively. Mean graft survival was significantly better in the LD transplants (14.0 years) compared to the DD transplants (8.0 years) (P = 0.013) (Table 2). However, donor type was not a significant predictor of graft survival after adjustment for gender, race, waiting time, recipient age at time of transplant,

Table 2. Comparison of Patients with LD and DD Transplants

Characteristics	Total (n = 42)	LD (n = 26)	DD (n = 16)	*P*
Gender (%)				0.751
Male	21 (50.0)	12 (46.2)	9 (56.3)	
Female	21 (50.0)	14 (53.8)	7 (43.7)	
Ethnic group (%)				0.105
Chinese	27 (64.3)	14 (53.8)	13 (81.3)	
Malay	10 (23.8)	7 (26.9)	3 (18.7)	
Indian	5 (11.9)	5 (19.2)	0	
Age at ESRD in years, median (range)	10.9 (2.6-20.9)	10.1 (2.6-20.9)	12.9 (3.0-20.5)	0.365
Age at transplant in years				
All, median (range)	13.9 (3.4-27.1)	12.5 (3.4-25.0)	16.4 (8.5-27.1)	**0.019**
2-6 years (%)	5 (11.9)	5 (19.2)	0	
6.1-11 years (%)	7 (16.7)	6 (23.1)	1 (6.3)	
11.1-15 years (%)	11 (26.2)	7 (26.9)	4 (25.0)	
15.1-20 years (%)	11 (26.2)	5 (19.2)	6 (37.5)	
>20 years (%)	8 (19.0)	3 (11.5)	5 (31.3)	
Waiting time in years, median (range)	2.2 (0.3-11.2)	1.5 (0.3-9.9)	4.9 (0.9-11.2)	**<0.001**
Follow-up time in years, median (range)	6.3 (0.07-18.9)	7.9 (0.2-18.9)	4.5 (0.07-18.02)	**0.027**
Maintenance dialysis before transplant				
Peritoneal dialysis only (%)	31 (73.8)	19 (73.1)	12 (75.0)	1.000
Haemodialysis only (%)	11 (26.2)	7 (26.9)	4 (25.0)	
Transplant performed overseas (%)	4 (9.5)	0	4 (25.0)	**0.016**
Immunosuppressive era (%)				1.000
1989-1997	14 (34.1)	9 (36.0)	5 (31.3)	
1998-2007	27 (65.9)	16 (64.0)	11 (68.7)	
Acute tubular necrosis (%)	7 (16.7)	1 (3.8)	6 (37.5)	**0.008**
Rejections (%)				
Early acute	4 (9.5)	1 (3.8)	3 (18.8)	0.146
Late acute	11 (26.2)	6 (23.0)	5 (31.3)	0.720
Chronic	11 (26.2)	8 (30.8)	3 (18.8)	0.485
Patient survival rates				
1 year (SE)	95.1 (3.4)	100	86.7 (8.8)	
5 years (SE)	92.1 (4.4)	95.5 (4.4)	86.7 (8.8)	
10 years (SE)	85.5 (7.5)	85.9 (9.9)	86.7 (8.8)	
15 years (SE)	85.5 (7.5)	85.9 (9.9)	86.7 (8.8)	
Overall patient survival time (y)	16.8 ± 1.0	17.2 ± 1.1	15.6 ± 1.6	
Mean ± SE (95% CI)	(14.9-18.7)	(14.9-19.4)	(12.6-18.7)	0.471
Graft survival rates				
1 year (SE)	92.8 (4.0)	100	80.8 (10.0)	
5 years (SE)	77.5 (7.2)	89.5 (7.1)	56.5 (13.6)	
10 years (SE)	58.7 (9.9)	67.3 (12.4)	42.4 (16.0)	
15 years (SE)	52.2 (10.7)	67.3 (12.4)	28.3 (15.7)	
Overall graft survival time (y)	11.9 ± 1.4	14.0 ± 1.5	8.0 ± 2.1	**0.013**
Mean ± SE (95% CI)	(9.2-14.6)	(11.1-17.0)	(3.8 – 12.1)	

CI: confidence interval; DD: deceased donor; ESRD: end stage renal disease; LD: living donor; SE: standard error;

Table 3. Causes of Graft Failure, Excluding Deaths (n = 10)

Causes	n
NSAID-induced acute nephrotoxicity	1
Late acute rejection	2
Chronic graft rejection	
Cell-mediated vascular rejection	2
Humoral-mediated rejection	1
Unknown	2
Cytomegalovirus infection	1
Graft thrombosis	1

NSAID: non-steroidal anti-inflammatory drug

immunosuppression era and adherence (Fig. 2). There was no significant difference in overall graft survival between the 2 immunosuppressive eras (11.3 years versus 8.9 years, $P = 0.90$). Comparing the 1- and 5-year survival rates in the 2 immunosuppressive eras, the rates for 1989 to 1997 were 92.9 ± 6.9% and 71.4 ± 12.1%, whereas for 1998 to 2007, the rates were 92.4 ± 6.9% and 78.8 ± 10.3%, respectively. Median age for graft loss was 18.9 years (range, 14.6 to 25.5). All 5 patients who had their transplants (all were LD) before 6 years of age had functioning grafts by the end of the study period, with a median follow-up duration of 8.8 years (range, 1.1-18.9).

Table 4. Comparison of Patients with Functioning and Lost Grafts

Characteristics	Total (n = 42)	Functioning grafts (n = 28)	Lost grafts (n = 14)	*P*
Gender, %				0.326
Male	50.0	42.8	64.3	
Female	50.0	57.1	35.7	
Ethnic group, %				0.365
Chinese	64.3	71.4	50.0	
Malay	23.8	17.9	35.7	
Indian	11.9	10.7	14.3	
Age at transplant in years				0.245
All, median (range)	13.9 (3.4-27.1)	13.3 (3.4-27.1)	15.5 (7.5-22.6)	
2-6 years, %	11.9	18	0	
6.1-11 years, %	16.7	14	21	
11.1-15 years, %	26.2	29	21	
15.1-20 years, %	26.2	18	42	
>20 years, %	19.0	21	14	
Maintenance dialysis immediately before transplant, %				0.459
Peritoneal dialysis only	73.8	78.6	64.3	
Haemodialysis only	26.2	21.4	35.7	
Type of transplant, %				0.098
LD	61.9	71.4	42.8	
DD	38.1	28.5	57.2	
Immunosuppressive era, %				0.039
1989-1997	34.1	22.2	57.1	
1998-2007	65.9	77.8	42.9	
Acute tubular necrosis, %	16.7	3.6	42.8	0.003
CMV disease, %	16.7	7.1	35.7	0.031
Non-adherence, %	28.6	14.3	57.1	0.009
Rejections, %				
Early acute	9.5	3.6	21.4	1.000
Late acute	26.2	3.6	71.4	<0.000
Chronic	26.2	10.7	57.1	10.002

Causes of graft failure are listed in Table 3. One patient lost her graft at 7.5 years post-transplant following use of a non-steroidal anti-inflammatory drug prescribed for dysmenorrhoea. Another lost his graft following CMV infection at 1.7 years post-transplant. Of note, 7 grafts were lost to either late acute or chronic rejections, both of which were significantly associated with non-adherence ($P = 0.006$ and $P < 0.001$ respectively).

There were 3 grafts from DDs that were lost within 3 months of transplant. One patient, at 7 days post-transplant, had graft thrombosis which probably occurred due to innate pro-thrombotic tendency, contributed by hypotension during anaesthesia. The other 2 were the patients with dengue haemolytic uremic syndrome and thrombotic thrombocytopaenic purpura from *Escherichia coli* sepsis. Excluding these 3 episodes of early allograft loss, there was no significant difference in graft survival between LD and DD transplants ($P = 0.128$).

Earlier immunosuppressive era, late acute or chronic rejections, CMV disease and non-adherence were associated significantly with graft loss (hazard ratio, 69.8; 95% CI, 3.6-518.5; $P = 0.043$) (Table 4).

Rejection Episodes

As shown in Table 2, there were 4 episodes of early acute rejection, of which 3 were in DD allograft recipients. Twenty patients (47.6%) had late acute or chronic rejections, both of which were significantly associated with graft failure ($P < 0.001$ and $P = 0.003$ respectively). Of the 11 patients with late acute rejections, 9 of them were non-compliant with their medications. One patient had a late acute rejection episode as a result of a decrease in immunosuppressive medications due to post-transplant lymphoproliferative disease.

Surgical Complications

Early surgical complications included ureteral leak, ureteric necrosis leading to hydronephrosis, ureteric misanastomosis to uterus accompanied by urine leak from bladder perforation, retroperitoneal bleed, chylous leak, perinephric abscess and retroperitoneal abscess. Late surgical complications included hydronephrosis secondary to ureteric stenosis, severe grade vesicoureteric reflux resulting in recurrent pyelonephritis, renal artery stenosis and bladder calculi (Table 5).

Infectious Complications

Infectious complications are shown in Table 6. Bacterial infections occurred in 18 patients (42.9%), of which 11 patients (61.1%) had urinary tract infections mostly related to the presence of double-J stents in the immediate post-transplant period, while 1 patient had *Staphylococcus aureus* perinephric abscess from a surgical drain. One patient who had septicaemia within 1 month of transplant had *Eschericiae coli* sepsis and thrombocytopaenic purpura leading eventually to death. One patient with an overseas DD transplant contracted chronic hepatitis B and hepatitis C, but had normal liver function even after 18 years. Two patients probably had donor-transmitted dengue infections in the immediate postoperative period.[3] Seven (16.7%) patients had CMV disease. There was a trend of decreasing CMV incidence in the second immunosuppressive era (11.0%) compared to the first era (28.5%), although this was not statistically significant ($P = 0.205$). Manifestations of CMV disease in our patients were mainly pneumonitis, retinitis, colitis, hepatitis and encephalitis. Pneumonitis was severe in 1 patient, resulting in respiratory failure and eventually death. One patient had post-encephalitis epilepsy. Four of these 7 transplants were from CMV-positive donors to CMV-negative recipients, while the rest were CMV-positive donors to CMV-positive recipients. All patients had received prophylactic intravenous immunoglobulins,

Table 5. Surgical and Medical (Non-infectious) Complications (n = 42)

Complications	No. of patients	(%)
Surgical (early)		
Ureteral leak	2	(4.8)
Ureteric necrosis and hydronephrosis	1	(2.4)
Ureteric misanastomosis and bladder perforation	1	(2.4)
Chylous leak	2	(4.8)
Retroperitoneal bleed	2	(4.8)
Surgical (late)		
Ureteric stenosis and hydronephrosis	3	(7.1)
Grade V VUR and recurrent pyelonephritis	1	(2.4)
Chronic urinary calculi	2	(4.8)
Renal artery stenosis	2	(4.8)
Recurrence of primary disease	4	(9.5)
Renal vein thrombosis	3	(7.1)
Lymphoproliferative disease	3	(7.1)
Haemolytic uremic syndrome	2	(4.8)
Growth retardation (<3rd centile)	17	(40.5)
Chronic allograft nephropathy	18	(42.9)
Drug-induced		
Neurotoxicity (tacrolimus)	2	(4.8)
Type 2 diabetes mellitus (tacrolimus)	2	(4.8)
Gout (cyclosporine)	1	(2.4)
Microangiopathic haemolytic anaemia (cyclosporine)	1	(2.4)
Alopecia areata (cyclosporine)	1	(2.4)
Hepatitis (diltiazem)	1	(2.4)

VUR: vesicoureteric reflux

Table 6. Post-transplant Infections

Time post-transplant	Infection	No. of episodes
<1 month	Urinary tract infection	11
	Peritonitis	2
	Septicaemia	2
	Retroperitoneal abscess	1
	Perinephric abscess	1
	Cytomegalovirus disease	1
	Dengue	2
1-6 months	Urinary tract infection	2
	Septicaemia	2
	Pneumonia	1
	Pneumocystis pneumonia	1
	Ebstein-Barr virus	1
	Cytomegalovirus disease	3
> 6 months	Urinary tract infection	3
	Pneumonia	2
	Cutaneous abscess	2
	Chronic Hepatitis B	1
	Chronic Hepatitis C	2
	BK virus	2
	Ebstein-Barr virus	5
	Cytomegalovirus disease	3

and all except 2 of the CMV-positive recipients received prophylactic antiviral drugs after the transplant.

Non-infectious Complications

Non-infectious complications included recurrent IgA nephropathy, recurrent FSGS, recurrent membranous nephropathy, and vascular thrombosis resulting in graft loss (Table 5). Three patients developed post-transplant lymphoproliferative disease (PTLD), all of which were associated with Ebstein-Barr virus infection, at 17 months, 33 months and 11 years post-transplant. The former 2 were treated successfully with decrease in their immunosuppressive medications, while the latter eventually died of PTLD 2 months after the study period. Several patients developed complications from their immunosuppressive medications, including type 2 diabetes mellitus (tacrolimus), gout (cyclosporine), hepatitis (diltiazem), microangiopathic haemolytic anaemia (cyclosporine) and alopecia areata (cyclosporine).

Among the 28 functioning grafts at the end of the study, the median estimated GFR was 74.5 mL/min/1.73m^2 (range, 15.2 to 115.5 mL/min/1.73m^2) with no significant difference between the LD and DD transplants (74.5 versus 75.1 mL/min/1.73m^2, P = 0.98). Twenty-one (75%) patients had GFR of at least 60 mL/day/1.73m^2. However, 25 (89%) of these 28 patients with functioning grafts had hypertension, and the mean number of anti-hypertensive medications needed was 1.4 ± 0.8. The median pre- and post-transplant height standard deviation score (SDS) was -0.9 (range, -5.0 to 4.9) and -1.2 (range, -5.5 to 0.5), respectively. Final adult post-transplant height SDS correlated significantly with the pre-transplant height SDS (r = 0.724, P <0.0001). Rehabilitation of patients in our programme has been excellent, with 97.6% of patients returning to school to continue their education or returning to employment at the end of the study period.

Discussion

In this retrospective cohort study, all patients in the Paediatric Renal Replacement Programme who received a kidney transplant in Singapore or were managed within the first 3 weeks following an overseas transplant during the period of 1989 to 2007 were included. Similar to the North American experience, 38% of our patients received organs from a DD, while 52% were from a parent.[4,5] The remaining 10% received kidneys from other living-related donors.

In the first 10 years, 71.4% of the transplants performed in our centre were LD transplants, as the DD transplant programme was started only in December 1994. Overall, the median waiting time of our patients for DD kidneys (4.9 years) was 2.8 times longer compared to that of their North American counterparts (median 1.7 years).[4] This could be explained by the relatively small number of children on the waiting list compared to the adults, and the lack of priority for these young patients.

Our graft survival rates for recipients of LD transplants were excellent at 100% and 89.5% at 1 and 5 years post-transplant respectively. This is comparable to, if not slightly better than, the corresponding reported rates from North America which were 92.2% and 79.7%, respectively.[4] In contrast, our 1 and 5-year survival rates for recipients of DD transplants were worse at 80.8% and 56.5% respectively compared to the North American rates at 83.6% and 65.1%.[4] Possible contributing factors could be our relatively longer waiting times. Additionally, 13% of DD transplants in North America are pre-emptive transplants, unlike in Singapore where ESRD patients are placed on the waiting list only after dialysis has been instituted.[4] Furthermore, the better DD allograft survival rates in North America could be related to the priority given to paediatric patients.[4]

The overall actuarial graft survival times were significantly different between the LD and DD transplants (median, 14.0 years versus 8.0 years). However, when adjusted for various possible confounding factors, the donor type was not significant. The 1- and 5-year graft survival rates for the 2

immunosuppressive eras did not differ significantly, although there was a trend towards better graft survival in the later era. This was likely due to the improvement in immunosuppressive drugs such as tacrolimus, mycophenolate mofetil, as well as greater centre experience. Induction therapy was practiced in both eras, with the more specific anti-IL-2R antibodies being used as the first choice in the later era rather than OKT3 or anti-thymocyte globulin.

Previous studies identified cold ischaemic times of more than 24 to 36 hours as a contributing factor towards risk of graft loss.[6,7] However, in our cohort, this was probably not an important factor as the cold ischaemic times of all our DD transplant recipients were less than 25 hours, due to our small country size. Non-adherence to medications was a major significant factor for graft loss. Fifty-seven per cent of patients who lost their grafts were non-adherent to medications. This is in contrast to the North American paediatric population where non-adherence apparently contributed to only 4.4% of graft loss.[8] Overall, we had a non-adherence prevalence rate of 29%. Previous studies have reported rates of non-adherence of between 30% to 60%, the highest occurring in adolescents.[9] In our cohort, although there was no significant difference in the graft survival between those who received their transplant during adolescence versus those in the non-adolescent years, 42% of allograft failure occurred between the ages of 15 to 20 years, and the median age of graft loss was 18 years (range, 14 to 25). On the other hand, the outcomes of the 5 patients who had their transplant below 6 years of age appeared to be excellent, with none of them losing their grafts. The better outcomes in this younger age group could be partly attributed to the excellent adherence to medications by the parents, as well as to the fact that all of them were LD transplants.

Multivariate analysis showed, interestingly, that male sex, ATN and late acute rejections were significantly associated with graft failure. Males tended to fare worse than females in our cohort, in contrast to the data in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS),[4] where males tended to have primary diagnoses with better outcomes. One possible explanation for our finding was the increased non-adherence rate among the males, though this did not reach statistical significance. On the other hand, ATN and late acute rejections has been well-reported to be important predictors of graft failure.[6,10] A major limitation of this study is the small sample size. This resulted in the extremely large 95% confidence intervals in the calculation of the hazard ratios in the Cox regression model. The small sample size can also lead to inadequate power in the analysis of outcomes in our programme.

Complications related to infections were prominent in our cohort, especially donor-acquired infections. CMV disease was the most common opportunistic infection occurring in our transplant cohort, with an incidence rate of 17%, slightly higher than reported rates of 6% to 12% in most studies.[11] Fifty-seven per cent of patients in our cohort with CMV disease were CMV negative, and had received their allografts from CMV positive donors. This was consistent with reports that patients receiving a CMV positive graft were at increased risk for CMV disease, with the highest risk among patients CMV naive at the time of transplant. In addition, those who had CMV disease were more likely to lose their grafts compared to those who did not have CMV disease.[11] Among the 7 patients who had CMV disease, 1 patient died from the infection, 1 lost his graft, and 1 developed epilepsy secondary to CMV encephalitis, despite the fact that the latter 2 had received intravenous immunoglobulins and ganciclovir prophylaxis during the peri-transplant period. The patient who died of CMV disease was not CMV naive and hence did not receive intravenous immunoglobulins but had ganciclovir prophylaxis during the immediate post-transplant period. Indeed, it has been shown that the use of prophylactic immunoglobulins and antiviral drugs may not decrease CMV infection rates, though it does decrease major organ involvement.[11] The incidence of CMV disease was lower in the later immunosuppressive era (11% versus 28.5%) most probably due to a decrease in the immunosuppression protocol in the later era. In fact, all the patients who developed early CMV infection within the first 3 months post-transplant were from the earlier era where OKT3/anti-thymocyte globulin were used as induction agents, rather than anti-IL-2R antibodies.

PTLD occurred in 3 patients (7%). This was a higher rate than previously reported in 2 large series in paediatric renal transplant populations.[12,13] Two of these patients were on tacrolimus while the third was on cyclosporine, consistent with reports that the incidence of PTLD is higher with the use of tacrolimus.[14] In our cohort, the more adherent patients appeared to have a higher risk of PTLD as 10% of adherent patients developed the disease. This could be related to the higher degree of immunosuppression in this group of patients.

Early surgical complications (19%) were similar to the reported rates of up to 20% in other paediatric transplant populations.[15-17] More importantly, there were significant long-term morbidities as a result of these surgical complications such as hydronephrosis, recurrent pyelonephritis and renal artery stenosis, which resulted in compromised graft function.

There were no deaths secondary to cardiovascular disease, although cardiovascular morbidities were prevalent in our patients. A large percentage (89%) of our transplant

recipients had hypertension and 2 patients had type 2 diabetes mellitus as a result of immunosuppressive medications. It has been well-reported in the literature that cardiovascular deaths account for one-fourth of deaths among children with ESRD.[18] The absence of cardiovascular mortality was likely due to our small sample size.

In conclusion, our paediatric transplant programme being relatively small is faced with the challenge of maintaining our level of expertise and competence. As we approach the third decade of our programme, we are faced with problems similar to many larger transplant programmes such as patient adherence, opportunistic infections, drug-related morbidities and PTLD. Despite this, our overall long-term patient and graft survival rates for LD transplants are comparable to North American rates, although our DD transplant rates are slightly worse, probably a reflection of the transplant policies. In order to improve long-term outcomes, we have to develop strategies to improve patient adherence, and to encourage earlier as well as LD pre-emptive transplants.

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