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Long-Term Clinical Outcomes of Paediatric Kidney Transplantation in Hong Kong—A Territory-Wide Study

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ABSTRACT

Aim: To review the clinical characteristics and long-term outcomes of paediatric kidney transplants in Hong Kong.

Method: A retrospective cohort study was carried out on all paediatric kidney transplant recipients managed in the Paediatric Nephrology Centre in Hong Kong from 2009 to 2020. All recipients were under 21 at the time of transplant, with a minimal follow-up period of 2 years.

Results: Sixty-one patients (57.4% male; median age 13 years, IQR: 8.9–17.8) were followed for 6.4 years (IQR 4.3–9.6). The commonest causes of kidney failure were congenital abnormalities of the kidney and urinary tract (34.4%), followed by glomerular diseases (21.3%). 90.2% were deceased donor transplantation. Patient survival rates were 100%, 96.4%, and 96.4% at 1, 5, and 7 years, respectively, and the corresponding graft survival rates were 95.1%, 95.1%, and 89.9%. There were eight graft losses (13.1%). Rejection and chronic allograft nephropathy were the leading causes for graft loss after the first month. Donor age at or above 35 years and the presence of donor-specific antibodies with a history of antibody-mediated rejection (both $p < 0.05$) were associated with worse graft survival, while medication non-adherence was associated despite being marginally significant ($p = 0.056$). The rates of CMV syndrome and biopsy-proven BKV nephropathy were 19.7% and 13.1% respectively. 47.5% had short stature at the last follow-up.

Conclusion: Our paediatric kidney transplantation outcomes are favourable and comparable to international benchmarks. Preferential allocation of young donors below 35 to paediatric recipients, reinforce immunosuppressant compliance and early detection of DSA with prompt treatment of ABMR may improve allograft outcomes in paediatric recipients.

1 | Introduction

Kidney failure is an uncommon childhood condition with associated significant morbidity and mortality compared to the healthy paediatric population [1]. While there are considerable geographical variations in the incidence of kidney failure, we previously reported a local kidney failure incidence of 6.3 per million age-related population with an increasing trend over the last two decades [1]. Kidney transplant is the treatment of choice for patients with kidney failure in both paediatric and adult populations. Indeed, there was a 12-fold higher risk of developing mortality among patients who did not receive a kidney

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transplant [1]. While there is a growing body of literature on the short- and medium-term outcomes of kidney transplant in children in China [2], longer-term post-transplant outcomes such as patient and graft survivals, infection, rejection, and growth remain to be limited.

The aim of this study was to provide a comprehensive evaluation on the outcomes of kidney transplants in Hong Kong, exploring not only the graft survival but also complications and growth of our transplant recipients.

2 | Methods

2.1 | Study Design

We conducted a single-centre retrospective cohort study on patients who received kidney transplants from January 2009 to December 2020 and were managed at the Paediatric Nephrology Centre of Hong Kong Children's Hospital. Our centre was formerly located at Princess Margaret Hospital, Hong Kong. The Paediatric Nephrology Centre is the designated referral centre for complicated kidney disease, chronic dialysis and kidney transplant for children in Hong Kong. All patients under 21 years at the time of transplant with a minimum of 2 years' follow-up data were included for analyses. Data including patients' demographics, clinical presentations, laboratory findings, treatment and outcomes were retrospectively obtained from electronic medical records till December 2022. Regarding the follow-up schedule, patients were seen at 1–2 weeks' interval in the first 2 months, then every 4–8 weeks afterwards. In each follow-up visit, complete blood picture, liver and kidney biochemistry, 12-h trough tacrolimus (TAC) levels, growth parameters, drug compliance, and clinically significant events such as infections were assessed. Patients' height percentiles and *Z* scores of our patients' height were generated [3] at the time of transplant and the last review date. Underweight and overweight/obesity in children below 18 years of age was defined as having age-gender-specific BMI percentile <5th and ≥ 85th respectively. For recipients reaching adulthood, underweight was defined as BMI <18.5 and overweight was defined as BMI ≥ 23. Glycaemic and lipid profiles were evaluated yearly. Post-transplant diabetes mellitus (PTDM) was diagnosed with a 2-h glucose level greater than 11.1 mmol/L by oral glucose tolerance test (OGTT).

The study was approved by the Institution Research Ethics Review Board of the Hong Kong Children's Hospital, Hospital Authority (HKCH-REC-2020-011).

2.2 | Treatment—Immunosuppressive Regimens

All kidney transplant recipients (KTR) received protocolised immunosuppressive treatments. Standard immunosuppressants comprised corticosteroids, tacrolimus (TAC) and mycophenolate mofetil (MMF). Anti-IL2R induction was prescribed at the physician's discretion based on immunological risks such as the number and type of HLA mismatches between donor and recipient. All KTRs received a pulse of methylprednisolone (600 mg/m^2) followed by oral prednisolone(2 mg/kg/day) or equivalent, which was gradually tapered to 5 mg/m^2/day over a course of 6 months. We targeted the TAC 12-h trough level at 8–12, 7–10, and 5–8 ng/mL, respectively at week 1–4, 5–16, and beyond 16 weeks. MMF was commenced at 600 mg/m^2/dose twice daily, then tapered to half by week four. Alternatively, the immunosuppressive agents were substituted with cyclosporin and/or azathioprine in selected patients. Anti-thymocyte globulin (ATG) induction was given to only one patient who received a second transplant.

2.3 | Prophylaxis for Infective Complications

All patients were given co-trimoxazole prophylaxis for pneumocystis jiroveci pneumonia (PJP) in the first year post-transplant unless contraindicated, while patients with G6PD deficiency were offered monthly pentamidine inhalation. Cytomegalovirus (CMV) prophylaxis was given according to the risk of CMV reactivation as follows: universal valganciclovir was given for 6 months in high-risk patients (i.e., donor-positive [D+]/recipient-negative [R−]). CMV prophylaxis for intermediate-risk (i.e., [D+ or D− to R+] or low-risk [D−/R−]) was administered as per physicians' discretion. Regular surveillance of serum CMV PCR, Epstein–Barr virus (EBV) PCR, and BK virus PCR was regularly performed during the first-year post-transplant and then yearly thereafter.

2.4 | Outcome Measures

The primary outcomes were the patient and graft survivals at 1, 5, and 7 years after kidney transplant. Graft failure was defined as the need of dialysis. Early graft loss (EGL) was defined as the loss of graft function within the first 30 days of transplant. Graft survival was censored at death or the last follow-up.

Secondary outcomes included complications after transplant, namely, eGFR, rejection, infection, body height, and diabetes upon the last follow-up. Transplant waiting time was defined as the duration of pretransplant dialysis. Acute tubular necrosis (ATN) referred to the requirement of dialysis in the first week after transplant [4]. In our centre, we performed graft biopsy by indications, and mostly for graft dysfunction. Cellular rejections or antibody-mediated rejections (ABMR) were histologically biopsy-proven and classified according to BANFF Classification of Allograft Pathology. Early rejections referred to those that occurred within the first year after transplant [5]. T-cell mediated rejection was managed with three pulses of methylprednisolone (10 mg/kg) while patients with ABMR were treated with combinations of IVIG (total 2 g/kg), rituximab (375 mg/m^2) and plasmapheresis (4–6 sessions of 1–1.5 plasma volume) at the physicians' discretion.

Self-reported drug adherence (i.e., having taken more than 80% of the prescribed medication) was also documented during clinic visits [6]. Estimated glomerular filtration rate (eGFR) was calculated using the modified Schwartz formula for children below 18 years of age. For patients aged 18 or above, their eGFR was generated with the average of Schwartz and the CKD-EPI formula [7]. The slope of eGFR decline was calculated based on the assumption that it was a linear regression, using the eGFR at the last review date and at 1-year post-transplant when presumably a

steady state had been achieved [8]. CMV syndrome was defined as CMV viraemia with symptoms such as fever, leucopenia, thrombocytopenia, or raised liver enzymes. BK nephropathy (BKVN) was documented with biopsy-proven histology results.

2.5 | Statistical Analysis and Ethical Consideration

In this study, statistical analysis was performed by IBM SPSS statistics version 29 software, and a two-tailed *p*-value of less than 0.05 was considered statistically significant. The characteristics of the patients were examined by descriptive statistics.

Categorical variables were compared using chi-square or Fisher's exact tests where appropriate. Continuous variables were analysed by Student's *T*-tests or Mann–Whitney *U* tests where appropriate. Graft survival rates were estimated by the Kaplan–Meier survival analysis, and log-rank tests were applied to compare any significant difference in survival rates between different groups. A mixed-design ANOVA was adopted to explore how the trend of certain continuous variables would differ as a function of particular nominal categories.

3 | Results

3.1 | Patient Characteristics

A total of 61 KTRs (57.4% male; median age at kidney transplant 13.0 years, IQR: 8.9–17.8) were included in the study. The median follow-up time after transplant was 6.4 years (IQR 4.3–9.6) and the median age at evaluation was 21.9 years (IQR 16.5–26.1). Three patients were lost to follow up due to emigration. Fifty-five (90.2%) received deceased donor transplant (DDT) whereas six (9.8%) had living-related transplant (LRT). The leading cause of kidney failure in this cohort was congenital anomalies of kidney and urinary tract (CAKUT) (34.4%), followed by glomerular causes (21.3%). Hereditary/familial nephropathies accounted for 13.1% of the KTRs (Table 1).

Peritoneal dialysis (PD) was the major modality of kidney replacement therapy (KRT) prior to kidney transplant (65.6%). The median waiting time for DDT and LRT was 2.4 years (IQR 1.0–3.9) and 0.5 years (IQR 0–4.2), respectively. More than two-thirds of our DDT recipients had > 3 HLA mismatches, while 20% had six-antigen mismatches. The median donor age for DDT and LRT was similar at 40 (IQR 21–48.5) and 46.5 (IQR 43.75–47) respectively.

3.2 | Clinical Outcomes

3.2.1 | Patient Survival

Four patients died during the study period of 478.4 patient-years, corresponding to an estimated crude mortality rate of 8.4 per 1000 patient-years. The overall patient survival was 100%, 96.4%, and 96.4% at 1-, 5-, and 7-years, respectively. The causes of death were infection ($n = 3$) and acute T-lymphoblastic leukaemia ($n = 1$) (Table 2). One lost his kidney graft due to medication non-adherence and succumbed 4.3 years later due to severe peritonitis. The remaining three patients died with a functional graft.

3.2.2 | Graft Survival

There were eight graft losses during the study period (Table 3). Two patients (25%) had EGL within the first month: one due to vascular thrombosis and the other due to recurrent FSGS. Rejection and chronic allograft nephropathy accounted for the rest of the graft losses. The median time-to-graft loss was 5.8 years (IQR 0.75–8.2).

The overall death-censored graft survival was 95.1%, 95.1%, and 89.9% at 1-, 5-, and 7-years, respectively. Graft survival rate for DDT at 1, 5, and 7 years was 94.5%, 94.5%, and 89%, whereas the graft survival rate for LRT was 100% at 1, 5, and 7 years (Table 4). Upon Kaplan–Meier analyses, donor age ≥ 35 years and the development of circulating DSA with ABMR were associated with poor graft survival (log-rank test $p < 0.05$ for all; Figure 1a,b). Poor drug compliance was also marginally significantly associated with worse graft survival ($p = 0.056$; Figure 1c). The recipients' gender, age, source of kidney (LRT vs. DDT), CMV viraemia or syndrome, BK viraemia and BK nephropathy were not associated with graft survival in this cohort (all $ps > 0.10$). Among the 53 patients with a functioning graft at last follow-up, the overall mean rate of eGFR decline during the study period was 0.5 mL/min/1.73 m^2 per year. As for the 40 patients (65.6%) who had a functioning graft at 5 years, 15% had an eGFR < 30 mL/min/1.73 m^2.

3.2.3 | Short- and Long-Term Kidney Allograft Outcomes

Seven patients (11.5%) had delayed graft function (DGF) after kidney transplant. A total of 33 rejection episodes occurred in 19 KTRs (31.1%) (Table 5). 52.6% (10/19) of the first rejections occurred within the first year of transplant, all of which (10/10) were T-cell mediated rejection diagnosed at a median of 117.5 days (IQR, 73.5–176.3) after kidney transplant. 21.2% (7/33) rejection episodes were ABMR with a median onset of 750 days (IQR, 458–1252.5). Among those with a functioning graft at the last review, KTRs with any episodes of rejection had a lower median eGFR (40.8 mL/min/1.73 m^2, IQR 22.8–49.6) compared to those who did not experience any rejection episodes (68.0 mL/min/1.73 m^2, IQR 51.5–77.5). The proportion of KTRs with medication non-adherence was significantly higher in those with rejection compared with patients who did not develop a rejection (47.3% vs. 7.1%, RR 3.68, $p < 0.001$).

Histology features of calcineurin-inhibitor toxicity were also detected in 12 KTRs (19.7%).

3.2.4 | Infective Complications

There were 21 DNA viral infective episodes (Table 5). 80.9% (17/21) of the viral infections occurred within the first year of transplant. CMV syndrome was diagnosed in 12 KTRs (19.6%), of which 8 (66.7%) were in the high-risk group (D+/R−). Their overall median time of onset of CMV viraemia was 126 days (IQR 36.8–156) after kidney transplant. KTRs from the intermediate risk group (D+/R+) experienced CMV viraemia earlier than the high-risk group (median 134 vs. 34.5 days), all of whom were not on anti-viral prophylaxis at diagnosis. BKV viraemia was

TABLE 1 | Clinical characteristics of paediatric kidney transplant recipients.

Characteristic	Total ($n = 61$)	DDT ($n = 55$)	LRT ($n = 6$)
Gender			
Male	35 (57.4%)	32 (58.2%)	3 (50%)
Female	26 (42.6%)	23 (41.8%)	3 (50%)
Ethnicity			
Chinese	59 (96.7%)	53 (96.4%)	6 (100%)
Non-Chinese	2 (3.3%)	2 (3.6%)	0
Age at transplant (years)			
All, median (IQR)	13.0 (8.9–17.8)	13.0 (8.8 = 17.6)	15.2 (11.9–17.7)
< 12	29 (47.5%)	27 (49.1%)	2 (33.3%)
≥ 12	32 (52.5%)	28 (50.9%)	4 (66.7%)
Follow-up time in years, median (IQR)	6.4 (4.3–9.6)	6.5 (4.4–9.7)	6.3 (3.2–8.2)
Age at last review (years), median (IQR)	21.9 (16.5–26.1)	21.9 (16.6–26.2)	22.9 (17.2–24.4)
Aetiology of primary disease (%)			
CAKUT	21 (34.4%)	19 (34.5%)	2 (33.3%)
Glomerulonephritis	13 (21.3%)	12 (21.8%)	1 (16.7%)
Hereditary	8 (13.1%)	8 (14.6%)	0
Miscellaneous/unknown	19 (31.1%)	16 (29.1%)	3 (50%)
Maintenance dialysis before transplant			
Peritoneal dialysis (%)	40 (65.6%)	37 (67.3%)	3 (50%)
Haemodialysis (%)	18 (29.5%)	18 (32.7%)	0
Pre-emptive (%)	3 (4.9%)	0	3 (50%)
Transplant characteristics			
Waiting time in years, median (IQR)	2.4 (1.0–3.9)	2.4 (1.2–3.9)	0.5 (0–4.2)
Median donor age (years) (IQR)	41 (21–48)	40 (21–48.5)	46.5 (43.0.75–47)
Expanded criteria donor	5 (8.2%)	5 (9.0%)	0
No. of mismatches			
Zero HLA mismatches (%)	0	0	0
Six HLA mismatches (%)	13 (21.3%)	10 (20%)	0
≤ mismatches	19 (31.1%)	13 (23.6%)	6 (100%)
> 3 mismatches	42 (68.9%)	42 (76.4%)	0
Cold ischemic time			
≤ 18 h (%)	53 (86.9%)	47 (85.5%)	6 (100%)
> 18 h (%)	4 (6.6%)	4 (7.3%)	0
Risk of CMV			
Low risk	11 (18.0%)	11 (20%)	0
Intermediate risk	24 (39.3%)	20 (36.4%)	4 (66.7%)
High risk	25 (41.1%)	23 (41.8%)	2 (33.3%)
Unknown	1 (1.6%)	1 (1.8%)	0

(Continues)

TABLE 1 | (Continued)

Characteristic	Total ($n=61$)	DDT ($n=55$)	LRT ($n=6$)
Choice of IS at transplant			
With induction	15 (24.6%)	15 (27.3%)	0
AZA + Cyc A	1 (1.6%)	1 (1.8%)	0
MMF + Cyc A	2 (3.3%)	2 (3.6%)	0
AZA + FK	18 (29.5%)	16 (29.1%)	2 (33.3%)
MMF + FK	40 (65.6%)	36 (65.5%)	4 (66.7%)
Non compliance	12 (19.7%)	9 (16.4%)	3 (50%)

observed in 23 (37.7%) of our patients, and 8 patients (13.1%) had biopsy-proven BKV nephropathy. These patients were managed with a reduction in immunosuppressants, IVIG, and some with adjunctive treatment. There were no graft losses in patients with BKVN, and 62.5% (5/8) had documented clearance of the BKV viraemia. Transient EBV viraemia occurred in 14 patients (23.0%), and one patient had EBV disease presenting with a tongue ulcer who improved with adjustments of immunosuppressants.

Urinary tract infection (UTI) occurred in 23 patients (37.7%). Among them, 3 had documented graft vesico-ureteric reflux (VUR). Six patients (9.8%) contracted PJP at a median duration of 1418.5 days (IQR 782.3–2776.3) from the time of transplant. There was one KTR (G6PD deficient) who suffered from PJP at about 3 months post-transplant despite pentamidine prophylaxis.

3.2.5 | Growth and Metabolic Complications

Almost half of our cohort (47.5%) had short stature at the last follow-up. Kidney replacement therapy initiated at an earlier age (7.6 vs. 14.3 years; $p=0.01$), kidney transplant performed at an earlier age (11.4 vs. 16.7 years; p-0.02) and short stature at the time of the transplant ($p<0.001$) were factors significantly associated with short stature at the last review (Table 6). Nine patients received growth hormone (GH) therapy after transplant, 7 in the < 3rd percentile and 2 in the > 3rd percentile group, respectively. Sixteen patients (28.6%) demonstrated an increase in height z score post-transplant, though 8/16 of their final height remained at < 3% at the last review date. While 10 KTRs (16.4%) were underweight, 14 patients (23.0%) were overweight or obese at the time of the last review (Table 5). Five patients (8.2%) developed PTDM at a median of 3.6 years (IQR 2.1–3.9) post-transplant, and 4 of them required medical treatment to maintain adequate glycaemic control.

4 | Discussion

The number of paediatric kidney transplants performed in our centre was increased by three-fold from the previous (1992–2002) to present (2009–2020) era. In 2002, Tse et al. reviewed 20 paediatric kidney transplants in Hong Kong, and the graft survival among deceased kidney transplants were 92.3% and 83.1% at 1 and 3 years [9]. In this latest cohort, we report improved and favourable long-term patient and graft survival. However, while advances in immunosuppressive strategies improved kidney allograft outcomes, significant complications including infection and malignancy came in parallel and resulted in morbidity and mortality.

The overall patient survival was 96.4% at 5- and 7-years, which was comparable to various international studies that documented survival at 95.5%–99% [2, 10, 11]. The mortality rate among KRTs was lower than the paediatric dialysis population in our centre (8.4 vs. 17.3 per 1000 patient years) [1]. Mortalities were observed in 4 patients, including 3 patients with infection and 1 patient with acute T-cell lymphoblastic leukaemia (T-ALL). Malignancies (PTM) were increasingly recognised in the paediatric transplant population, with an incidence that ranged from 5.6% to 15.4% worldwide, increasing with the number of years post-transplant [12–14]. The Australian and New Zealand Transplant Registry reported the median time of death due to malignancy in their paediatric KTRs to be 19 years [13, 14]. The relative short duration of our study period might not reflect the true incidence of PTM, yet the awareness of PTM should be heightened among paediatric nephrologists, facilitating early detection and treatment.

Our overall graft survival of 95.1% at 1- and 5-years was comparable to that reported in North America, the UK, and Singapore [4, 14, 15], ranging from 92.8% to 98% at 1 year and 77.5% to 94% at 5 years. Three important factors were identified to be associated with improved graft survival in our cohort: absence of DSA and antibody-mediated rejection; drug compliance; donor age < 35 years old. The development of DSA and ABMR is prevalent in our cohort, probably potentiated by poor HLA matching with deceased donors. In our cohort, more than 3 HLA mismatches were associated with the development of DSA and ABMR (OR 1.15) but it was statistically insignificant ($p=0.88$). HLA mismatch is a crucial predictor of rejection and graft loss despite the use of modern-era immunosuppressants [16, 17]. About 66% of our DDT pairs had more than 3 mismatches, in contrary to 84% of the patients who received a well-matched kidney (0 mismatch/0 DR + 0/1 B mismatch) in the United Kingdom [15]. This is partly attributed to the long waiting time and low donation rates in Hong Kong, which is a major challenge. Compared to the US (0.78 years) and Australia (1.01 years) [18, 19], our median time to DDT was 2.4 years from the time that the child was enlisted. The importance of HLA matching in relation to the development of ABMR cannot be overemphasised, as the risk of

TABLE 2 | Details of four patients who died in the study period.

No.	Primary kidney disease	Age at kidney transplant (y)	Age at death (y)	Time since kidney transplant (y)	Functional graft (Y/N)	Cause of death
1	CAKUT	9.2	16.7	7.5	Y	Acute T-lymphoblastic leukaemia
2	Chronic glomerulopathy	17.9	22.2	4.3	N	Peritonitis with systemic sepsis
3	FSGS	19.4	28.8	9.4	Y	Pneumonia with respiratory failure
4	Chronic glomerulopathy	20.1	24.3	4.2	Y	Fungaemia (*Candida albicans*) with clinical sepsis

TABLE 3 | Clinical characteristics of patients with graft loss.

Patient				
Age at transplant (years)	Primary diagnosis	LRT/DDT	Cause of graft loss	Time of graft loss (days)
11.4	PH1	DDT	Renal vein and renal artery thrombosis with graft infarct	10
11.9	FSGS	DDT	FSGS recurrence	19
17.9	GN	DDT	Chronic rejection due to non-adherence	357
9.3	Dysplastic kidneys	DDT	Antibody mediated rejection	1954
16.8	ANCA associated GN	DDT	Chronic allograft nephropathy	2258
17.5	Alport syndrome	DDT	Chronic rejection due to non-adherence	2920
11.6	Reflux Nephropathy	LRT	Chronic allograft nephropathy	3217
20.8	Alport syndrome	DDT	Chronic allograft nephropathy	3404

TABLE 4 | Death-censored graft survival.

Graft survival	1 year	5 years	7 years
Overall	95.1% ($n=59$)	95.1% ($n=40$)	89.9% ($n=27$)
DDT	94.5% ($n=53$)	94.5% ($n=37$)	89% ($n=25$)
LRT	100% ($n=6$)	100% ($n=3$)	100% ($n=2$)

allograft loss has been shown to increase with each additional HLA mismatch [15–17]. Indeed, our incidence of acute rejection within the first year of transplant (16.4%), mostly T-cell mediated, was similar to that reported in North America (16%) [9] and Oceania (12%) [18]. Yet, an apparently higher rate of rejection of 31% over the whole study period was observed and attributed to a high proportion of late-onset rejection (16/33) especially ABMR (median onset 750 days), which was a significant predictor for developing graft failure. The findings also underscored the importance of monitoring DSA, even in stable KTR who had received kidney transplantation for a long time. Another important factor for developing DSA and ABMR is non-adherence. This is an important and potentially modifiable factor to reduce rejections [20]. Non-adherence was reported to be up to 45.5% in international paediatric KTRs [14, 20]. In our cohort, non-adherence was documented in 12 patients (19.7%), while 9 of them experienced at least one episode of rejection. The relatively better adherence in our cohort could be partly attributed to the Chinese culture, where parents and caretakers are heavily involved in the care of sick children. On the other hand, these children are also well supported by the dedicated renal nurses assigned to take care of them from the start of dialysis through transplant. The rapport between the nursing staff and the family permitted regular review of adherence, education, and support

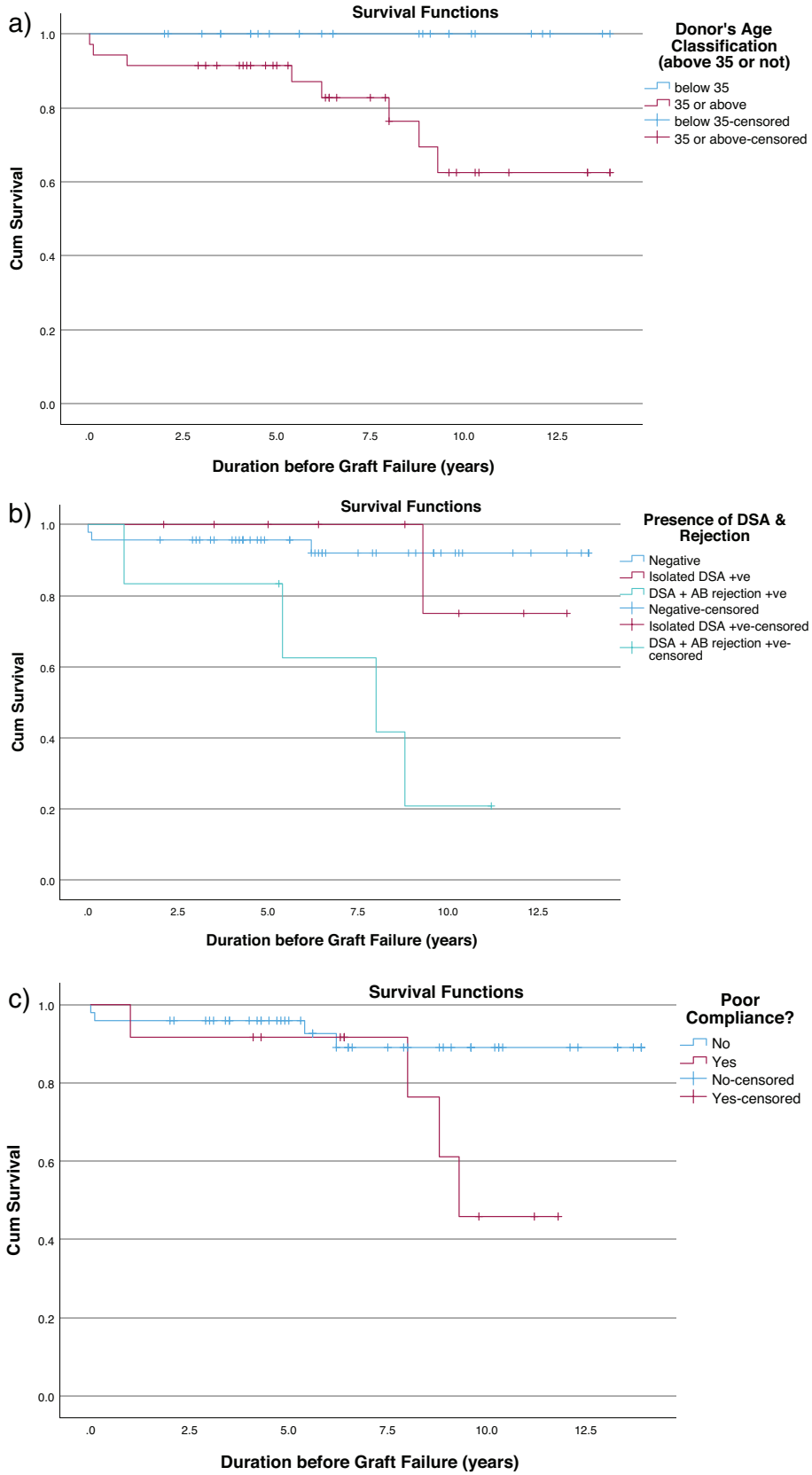

FIGURE 1 | Kaplan–Meier plot of paediatric allograft kidney survival by (a) donors' age below 35 yo ($p = 0.009$); (b) presence of DSA and rejection ($p < 0.001$); (c) medication adherence ($p = 0.56$).

TABLE 5 | Secondary outcomes of paediatric kidney transplant.

Secondary outcomes	Prevalence, *n* (%)	Median onset time (IQR)
Rejection episodes	33	
T-cell rejection	26	138.5 days (76.5–450)
Antibody mediated	7	750 days (440.5–1402.5)
No. of transplants with at least 1 rejection	19 (31.1)	
1st rejection within 1st year	10	117.5 days (73.5–176.3)
1st rejection after 1st year	9	919 days (649–1638)
Infection		
CMV syndrome	12 (19.7)	126 days (36.8–156)
CMV high risk	8	134 days (124.5–211.3)
CMV Intermediate risk	4	34.5 days (30.5–58.3)
BK nephropathy	8 (13.1)	191 days (160.8–1141)
EBV disease	1 (1.6)	113 days
UTI	23 (37.7)	n/a
PCP pneumonia	6 (9.8)	1418.5 days (782.3–2776.3)
Growth & metabolic		
Short stature	29 (47.5)	
Underweight	10 (16.4)	
Overweight/obese	14 (23.0)	
Post-transplant diabetes	5 (8.2)	3.6 years (2.1–3.9)

from the multidisciplinary team. However, we did notice that our KTRs with non-compliance had an older age at transplant (median 17.3 vs. 12.0), which correlated with previous studies that adolescents who needed to take care of their own medication was at a higher risk of non-adherence [20].

Regarding donor factors, young, deceased donor kidneys demonstrated survival benefits in various studies over old age donor kidneys due to multiple factors such as the better ability to mount a tissue repair process in case of kidney injuries or rejection [16, 21]. There could also be better functional adaptation of the young donor kidneys to the growth of the paediatric KTRs [17]. In fact, donor age was one of the important considered variables in the cadaveric kidney allocation system in many localities [18, 19]. Due to the scarcity of deceased donors and long waiting times prior to transplants, 21% of our deceased donors were above the age of 50 and was associated with considerably worse graft survival. Our data supported that priority in organ allocation, both in terms of graft quality and waiting time, should be given to paediatric patients. Furthermore, avenues to expand the donor pool, such as paired kidney donation program, ABO/HLA incompatible kidney transplants, could be considered to facilitate transplants in the paediatric population.

While transplant offers better survival and quality of life to children with kidney failure, it is also inevitably associated with complications. The CMV seroprevalence rate in the general paediatric population was approximately 50% in Hong Kong and increased with age [22]. With the CMV seroprevalence rate in this present cohort being marginally lower at 39.3%, the incidence of CMV viraemia and CMV syndrome was high at 41.0% and 19.7%, respectively. This was in contrast to that reported in the CERTAIN Registry in Europe [23], in which the overall rate of CMV syndrome during the first 3 years after transplant was as low as 5.0%, and in other single-centre studies the rate could range from 0% to 11.4% [24]. In our centre, KTRs were given valganciclovir prophylaxis according to the CMV risk status, but the dosage could be suboptimal as limited by adverse effects like neutropenia. The fact that all our KTRs were not on anti-CMV prophylaxis at the time of the onset of CMV viraemia supported the use of antiviral prophylaxis in both the intermediate and high-risk groups in the early post-transplant period when they are on intense immunosuppressant therapies. Close surveillance of CMV replication should also be implemented, especially upon cessation of antiviral prophylaxis, to detect late-onset CMV complications.

TABLE 6 | Analysis of growth after kidney transplant.

	BH < 3% (*n* = 29)	BH ≥ 3% (*n* = 32)	*p*
Prevalence (%)	29 (47.5)	32 (52.5)	
Age at dialysis, median (IQR)	7.6 (4.1–12.4)	14.1 (8.8–16.0)	0.01
Age at transplant, median (IQR)	11.4 (7.6–15.0)	16.7 (10.6–18.1)	0.02
Short stature (BH < 3%) at transplant, *n* (%)	26 (78.8)	7 (21.9)	< 0.001
eGFR at last review, median (range)	54.0 (43.3–75.6)	57.0 (41.8–73.5)	0.81
Use of growth hormone post-transplant, *n* (%)	7 (24.1)	2 (6.3)	0.07
Presence of rejection, *n* (%)	10 (34.5)	9 (28.1)	0.78

In recent years, BK virus has also been increasingly recognised as a significant opportunistic infection in kidney transplants, which could lead to cystitis, ureteric stenosis as well as BK nephropathy and later-on graft loss. BK nephropathy has a reported incidence of 1%–6.6% worldwide [25–27]. In our study, there was a high incidence of biopsy-proven BK nephropathy at 13.1%, which echoes the recent finding from Shanghai [28]. The mainstay of treatment was reduction of IS. This highlights the clinical conundrum to balance the risks between infection and rejection, and novel biomarkers or assays to personalise immunosuppressive loads in KTRs remains an unmet need.

Finally, growth retardation after transplantation was common because of poor graft function, steroid use, and lack of catch-up growth in adolescent KTRs. In this cohort, nearly half of our patients had short stature, similar to the findings in a European study where 44.9% of the 3492 transplanted patients had a growth deficit [29]. The high incidence rates of growth retardation in our series may be related to multiple factors. Over half of our patients had short stature at the time of the transplant and remained as such at the last review. Unfortunately, recombinant growth hormone therapy had not been a standard treatment post-transplant until the later part of our study [30]. Another reason was that steroid minimisation might not be possible in the face of poor HLA matching. In addition, with a median age of transplant at 13.0 years, many had already reached puberty, and catch-up growth was not demonstrated. It is important to optimise children's growth and nutrition during CKD or dialysis in order to facilitate better outcomes for these children.

There are several limitations to this study. Due to the retrospective nature of our study, there could be reporting bias. Second, about 21.3% of our patients received transplants at age beyond 18. Notwithstanding, our centre takes care of all paediatric transplant patients in Hong Kong, and all patients received standard management protocols with comprehensive follow-up data. Hence, our data was still able to provide real-world evidence on the outcomes of paediatric KTRs who are predominantly Chinese.

5 | Conclusion

Our data demonstrates substantial improvements in paediatric kidney transplant recipient (KTR) outcomes, including patient and graft survival, since the inception of our transplant program in 1992. Key factors associated with favourable outcomes include young donor age (< 35 years), absence of donor-specific antibodies (DSA) and antibody-mediated rejection (ABMR), and good patient adherence to medications. While establishing a successful paediatric transplant program faces inherent challenges, we believe implementing policies that prioritise children for transplantation is essential. In addition to preventing and closely monitoring for infection and rejection, optimising growth potential and metabolic profiles can further enhance the long-term outlook for our paediatric KTRs.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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