Long-term outcome of pediatric kidney transplantation: A single-center experience over the past thirty-four years in Japan

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Abbreviations

ABO-cKTx = ABO-compatible kidney transplantation

ABO-incKTx = ABO-incompatible KTx

ALG = antilymphocyte globulin

AR = acute rejection

AZA = azathioprine

BXM = basiliximab

CAKUT = congenital anomalies of the kidney and urinary tract

CAN = chronic allograft nephropathy

CI = confidence interval

CIT = cold ischemia time

CNIs = calcineurin inhibitors

CPM = cyclophosphamide

CsA = Cyclosporin A

DD = deceased donor

DGF = delayed graft function

DSG = deoxyspergualine

DWFG = death with a functioning graft

ESRD = end-stage renal disease

HD = hemodialysis

HLA = human leukocyte antigen

HR = hazard ratio

HUS = hemolytic uremic syndrome

IQR = interquartile range

IV = intravenously

KTx = kidney transplantation

LRD = living related donor

MMF = mycophenolate mofetil

MPL = methylprednisolone

MZR = mizoribine

PD = peritoneal dialysis

RRT = renal replacement therapy

SD = standard deviation

TMCMC = Tokyo Metropolitan Children's Medical Center

VIF = variance inflation factor

Abstract

Objectives: To evaluate long-term outcomes and graft loss risk factors of pediatric kidney transplantation over the past three decades.

Methods: We retrospectively assessed 400 consecutive kidney transplantation performed in 377 children from 1975–2009. Patients were stratified into three eras according to the introduction of immunosuppressive regimen (Era 1: methylprednisolone and azathioprine, Era 2: calcineurin inhibitors based therapy including methylprednisolone and azathioprine or mizoribine, Era 3: basiliximab induction therapy including calcineurin inhibitors, methylprednisolone and mycophenolate mofetil).

Results: The median age was 9.7 years and the median body weight was 20.6 kg at transplantation. 364 (91.0%) received a living related donor transplantation. The acute rejection rate within 1-year posttransplant declined significantly from 61.0% in Era 1 to 14.5% in Era 3 ($p < 0.001$). For transplant Eras 1–3, the 1-year graft survival was 81%, 93%, and 95%; the 5-year graft survival was 66%, 86%, and 93%; and 10-year graft survival was 47%, 79%, and 89%, respectively. The overall 5-, 10- and 20-year patient survival rates were 96%, 93% and 88%, respectively. A Cox multivariate analysis identified cold ischemia time (hazard ratio 1.002, 95% confidence interval 1.001–1.003)

and acute rejection (hazard ratio 1.314, 95% confidence interval 1.147–1.505) as independent risk factors for graft loss.

Conclusions: The progress of immunosuppressive therapy carried the low incidence of acute rejection and the high graft survival rate through over 30 years in pediatric transplantation.

Keywords Kidney transplantation, Pediatric, Graft survival, Mortality, ABO-incompatible

Introduction

ESRD is a rare and severe condition in children. Approximately, five to ten children per million in the age-related population are initiated on RRT yearly and the mortality rate in children with ESRD may be 30 times higher than in the age-related healthy population.[1,2] Recently, significant improvements have been achieved in short-term results of pediatric KTx, mostly due to improved peri- and postoperative care, availability of better immunosuppressant drugs, and better monitoring and management of infection. [3, 4] Moreover, the incidence of surgical complications, DGF, AR, and postoperative infections in pediatric recipients has decreased over the past 20 years.[5]

The long-term outcome of pediatric KTx is a major concern requiring adequate therapy and follow-up over several decades. [6-9] An important question raised by clinicians is how pediatric transplant recipients will manage in the long-term, after their transition to adult care. The answer is yet unclear and data on long-term outcomes of pediatric KTx are still limited. [6-9]

The aim of this study was to describe long-term outcomes over the past three decades in pediatric KTx.

Methods

Study design and patient population

This single-center retrospective study was conducted at the TMCMC. We reviewed the medical charts of all consecutive 400 KTx performed in patients aged 18 years or younger at the Tokyo Metropolitan Kiyose Children's Hospital (the predecessor of Tokyo Metropolitan Children's Medical Center) between January 1975 and December 2009. The majority of transplant recipients were transferred to the TMCMC and to the Toho University Omori Medical Center in Tokyo. Recipients were followed up from KTx until the last known date alive as of December 2016. Clinical data from recipients who were transferred to the centers were extracted from the medical records. The incidence of AR, graft and patient survival including these risk factors were evaluated in three eras according to the differences of immunosuppressive regimens. This study was approved by the central ethics board of the TMCMC (approval number; H28b-209) and the Toho University Omori Medical Center (approval number; M17126).

Immunosuppression

Immunosuppressive protocols were stratified according to three different time periods.

Era 1: 1975 to 1985

From 1975 to 1985, the immunosuppressive protocol consisted of MPL, AZA, and/or MZR. MPL tapered to a maintenance dose of 0.2–0.25 mg/kg/day for four months after KTx. AZA was administered at a maintenance dose of 1.5 mg/kg/day continuously. MZR was maintained for at least four weeks postoperatively, then tapered to a maintenance dose of 3 mg/kg/day.[10]

Era 2: 1986 to 2001

CNIs were utilized in Era 2. CsA introduced in June 1986, and Tac introduced in February 1997 were used. The immunosuppressive protocol consisted of MPL, AZA or MZR, and CsA or Tac. MPL was tapered to a maintenance dose of 0.2–0.25 mg/kg/day at four months and 0.2–0.4 mg/kg every other day at 1 year. CsA was started at 5 mg/kg/day on the day before KTx.A target trough level of CsA was 300–400 ng/mL (whole blood, FPIA) during the first few months, 150–200 ng/mL by month 4, and 120-150 ng/mL by 1 year post-Tx. Oral Tac was started at 0.3 mg/kg/day on the day before KTx, and IV Tac was administered until day 5 after KTx. The target trough level of TAC was 15–20 ng/mL during the first two months, 10–20 ng/mL by month 4, and 7–10 ng/mL by year 1 after Tx. AZA or MZR was given at 1.0–1.5 mg/kg/day or 2.0– 3.0 mg/kg/day, respectively.

Era 3: 2002 to 2009

From 2002, MMF and BXM were introduced. CsA was started at 8 mg/kg/day orally on the day before KTx. The target area under the blood concentration-time curve 0–4 levels of CsA was 4000 ng/mL during post-operative month 1, 3200–3500 ng/mL by month 4, and 2500–2800 ng/mL by year 1 then. Tac was started orally at 0.3 mg/kg/day on the day before KTx and was then administered IV until 5 days after KTx. The target trough levels were 10–13 ng/mL during the first month, 7–10 ng/mL by month 4, and 5–7 ng/mL by year 1 after KTx then. MPL dose was rapidly reduced to a maintenance dose of 4 mg on alternate days three months after KTx. MMF was administered preoperatively at a dose of 600–800 mg/m²/day and induction therapy consisted of BXM at days 0 and 4.

Data collection and clinical definitions

The extracted recipient and donor information included patient characteristics (recipient and donor), graft function, physical examination findings, medical history, patient and graft survival, cause of death, and graft loss. Graft function was monitored by serum creatinine values. The diagnosis of AR was normally based on the findings of a kidney allograft biopsy. AR was treated with bolus IV MPL (15–30 mg/kg/day), followed by increased oral steroid dose. An OKT-3 monoclonal antibody was added for 10 days when

AR was steroid-resistant. DGF was defined as the need for dialysis within one week after transplantation. Graft loss was defined as the resumption of dialysis, re-transplantation, transplant nephrectomy, or DWFG.

Statistical analysis

Categorical data were expressed as numbers with percentages, and continuous data were expressed as the mean ± SD and median with a range or IQR, depending on the normality of the distribution. Categorical data using the chi-square test or Fisher's exact test and continuous data using the Mann-Whitney U test were analyzed. Patient and graft survival were estimated using the Kaplan-Meier method. Graft half-life was calculated at the intersection point of the Kaplan-Meier survival curve with a survival threshold of 50%. Univariate and multivariate analyses were performed using the Cox proportional hazard regression model to determine the risk factors for graft loss and patient death. Variables with $p < 0.1$ in the univariate analysis were included in the multivariate analysis. The results were expressed as adjusted HR with a 95% CI, and a two-sided $p < 0.05$ was considered statistically significant. The statistical analyses were performed using SPSS software (version 22.0; SPSS Inc., Chicago, Illinois, USA) and R (version 3.2.4, The R Foundation for Statistical Computing, Vienna, Austria).

Results

Population characteristics

The main population characteristics are summarized in Table 1. 400 pediatric KTx were performed in 377 patients and 23 patients (6.1%) underwent re-transplantation. The median age was 9.7 years (range 1.6–18.8) and the median body weight was 20.6 kg (range 7.4–70.0) at KTx. The median duration of follow-up was 15.3 years (range 0.0–42.2), and the median age of the survivors at last follow-up was 26.3 years (range 8.7–57.6).

A total of 30 recipients (7.5%) underwent pre-emptive KTx and the remaining 370 recipients (92.5%) were on dialysis at the time of KTx. The median duration of dialysis before KTx was 22.3 months (range 0.2–118). The duration of dialysis increased from Era 1 to Era 3. 364 donors were LRD (91.0%) and 36 were DD (9%). The median age of the donors was 39 years (IQR 35–44) for LRD and 33 years (IQR 18-46) for DD. LRD had a statistically significantly lower CIT than DD (median 44 vs. 406 minutes, respectively, $p < 0.0001$).

The etiologies of ESRD are shown in Table 2. The most common cause of ESRD was CAKUT, including hypoplasia/dysplasia, reflux nephropathy, and obstructive uropathy.

Acute rejection

The incidence of AR episodes was decreased and delayed over time. In Era 1, AR episodes were experienced 61.0%. However, this proportion was reduced further to 41.6% in Era 2, and Era 3 decreased significantly to 14.5% (Log-rank: $p < 0.001$ and Wilcoxon: $p < 0.001$, respectively) (Fig. 1). Median time to AR episodes was 7 days (IQR 6–28) in Era 1 and 40 days (IQR 19-334) in Era 2. From Era 3, median time to AR episodes increased to 705 days (IQR 28-2544).

Graft survival

Overall graft survival was 90%, 82%, 72%, 60%, 50%, 42%, 34%, and 30%, at 1, 5, 10, 15, 20, 25, 30, and 35 years post-KTx, respectively. The overall graft half-life was 20.1 years. Graft half-life by transplant era increased from 9.7 years in Era 1 to 26.9 years in Era 2. The graft half-life was 9.3 years for DD kidney transplantation and 21.1 years for LRD kidney transplantation.

Transplant Era

Graft survival for transplant Eras is shown in Fig. 2. The graft survival rate improved in Eras 2 and 3 (Log-rank: $p < 0.001$ and Wilcoxon: $p < 0.001$, respectively) compared with Era 1. However, these rates did not differ significantly between Eras 2 and 3 (Log-rank: $p = 0.194$ and Wilcoxon: $p = 0.175$, respectively).

Donor type

For DD KTx, graft survival was 64%, 61%, 42%, 31% and 23%, at 1, 5, 10, 15, and 20 years post-KTx, respectively. For LRD KTx, graft survival was 92%, 84%, 75%, 63%, and 53%, at 1, 5, 10, 15, and 20 years post-KTx, respectively. Graft survival for LRD KTx differed significantly from that of DD KTx (Log-rank: $p < 0.001$ and Wilcoxon: $p = 0.018$, respectively). Since Eras 2 and 3, graft survival for DD KTx rose to 90%, 84%, and 59%, at 1, 5, and 10 years post-KTx, respectively.

Causes and risk factors of graft loss

Of the 400 pediatric KTx, 176 experienced failed graft function during the study period. The causes of graft loss by period are shown in Table S1 (Online Resource 1). The most common cause was CAN. DWFG occurred at the same frequency in all periods. AR was the most common cause within the first year post-KTx in Era1. In Era 3, the most common

cause of graft loss within the first year post-KTx was vascular complications because three recipients had vascular thrombosis.

Recipient and donor factors were analyzed for overall graft survival. The results of the univariate and multivariate analyses are shown in Supplementary Table S2 (Online Resource 2). Univariate analysis showed that HUS, re-transplants, ABO-compatibility, DGF, CIT, AR, donor type, donor sex, and transplant era were significant predictors of survival. Factors with $p < 0.1$ included in the multivariate analysis were cold ischemia time, AR, donor sex, and transplant era, all of which were found to be significant predictors of overall graft survival.

Patient survival

Overall patient survival is shown in Fig. 3. Patient survival improved from Eras 2 to 3 ($p < 0.001$ and $p = 0.005$, respectively) compared with Era 1 (Fig. 4). However, these rates did not differ significantly between Eras 2 and 3 ($p = 0.880$). Patient survival in LRD KTx was significantly higher than that of DD KTx ($p = 0.015$).

Causes of death and mortality rate

Of the 377 patients, 47 patients (12.5%) died during the study period. The main causes of death were infection 26% (12 patients) and heart disease 15% (7 patients). Causes of death stratified by transplant era are detailed in Table S3 (Online Resource 3). During follow-up, the median age at death was 23.0 years (range: 2.1–45.4). The median time between KTx and death was 8.4 years (range: 1 day to 31.0 years). Forty-seven of 377 patients died, and the mortality rate was 9.98 per 100 patient-years (95% CI 7.42–13.05). The mortality rates per 100 patient-years for Eras 1 to 3 were 1.85 (95% CI 1.26–2.61), 0.41 (95% CI 0.20–0.73), and 0.24 (95% CI 0.08–0.57), respectively. The mortality rates by transplant era were consistently lower than the rate for Era 1. For LRD and DD KTx recipients, the mortality rate per 100 patient-years was 0.68 (95% CI 0.49–0.92) and 1.72 (95% CI 0.64–3.72), respectively. For patients aged 3 years or younger and for patients with a bodyweight of 15 kg at KTx, the mortality rate per 100 patient-years was 0.39 (95% CI 0.08–1.14) and 0.58 (95% CI 0.29–1.04), respectively.

The recipient and donor risk factors were analyzed for overall recipient survival. The results of univariate and multivariate analyses are shown in Online Supplementary Table S4 (Online Resource 4). Univariate analysis showed that the re-transplants, DGF, CIT, donor type, and transplant era were significant predictors of survival. For factors

with $p < 0.1$ in multivariate analysis, re-transplants ($p = 0.025$) and CIT ($p = 0.023$) were found to be significant predictors of poor patient survival.

Discussion

In this study, we presented the long-term outcomes of a pediatric KTx cohort over approximately a 34-year period. The main findings were as follows: (i) the incidence of AR episodes was decreased and delayed over the progress immunosuppressive therapy; (ii) 10-year graft survival rate by Era 1 to 3 improved to 47, 79 and 89%; (iii) graft half-life exceeded 25 years with the introduction of CNIs; (iv) after pediatric KTx, patients had a 30-year survival rate exceeding 80%.

Short- and medium-term patient survival of pediatric KTx were consistently over 90% in several reports. [11-13] Regarding long-term patient survival, registry data from Australia and New Zealand showed that the long-term survival rate between 1963 and 2002 was 79% at 10 years and 66% at 20 years in patients aged < 20 years who survived their first KTx 2 years after commencement of RRT.[1] A report from the USRDS showed that the 20-year survival of patients aged < 21 years who received their transplantation between 1983 and 2006 was 66.4%. [11] Data from single-center and national cohorts showed that 15- to 20-year patient survival after pediatric KTx ranged 72–91%, [6-9] which is in line

with the data from the previous study demonstrating patient survival exceeding 80% at 30 years post-KTx, as calculated using the Kaplan-Meier method. In previous studies as well as our own, the major causes of death were infection, cardiovascular disease, and malignancies. [6, 11, 12]

The graft survival rate has markedly improved over the past decades. [5, 12, 13] Our study also showed improvement in short-term graft survival across the three transplantation eras. Long-term graft survival from a previous report was 45–72% at 10 years, 35–59% at 15 years, and 30–40% at 20 years. [6-9] The data from our study showed a long-term graft survival rate of 72% at 10 years, 60% at 15 years, and 50% at 20 years, with a graft half-life of 26.9 years for Era 2. Since the appearance of CNIs, the overall graft survival rate increased to 79–89% at 10 years and 72–75% at 15 years. Consistent with previous reports, a substantial increase in the graft survival rate was observed during the last period of our study. However, despite progress in transplant immunity and new immunosuppressive agents, the long-term graft survival rate did not differ significantly between Eras 2 and 3 in our study, and we reported that graft loss by CAN exceeded 80% from ten years post-KTx. The etiology of CAN is multifactorial and includes both immunological and non-immunological factors[14] and CAN remains the most common cause of graft loss. Several reports have identified important predictors of graft survival. Recipient age at KTx, AR,

donor type, and primary disease are associated with predictors of graft survival. [6,7,12] In our study, the independent predictors of graft survival were transplant era, donor sex, CIT, and AR.

Immunosuppressive drug treatment has been strengthen. In our study, the less frequent episode AR due to the introduction of CNIs and BXM resulted in better graft survival. Two multicenter prospective studies have reported the absence of an association among induction agents and reduction in AR episodes or graft loss in recipients in whom the immunosuppressive protocol included CNIs as the main drug. [15,16] The beneficial effects on the short-term graft survival outcomes with the use of BXM have been reported in previous studies. [17,18]

The retrospective nature of our analysis and the relatively small number of events are important limitations of our study. In our cohort, there was no systematic record of data on kidney function or the social outcomes after KTx. Moreover, since fewer patients were alive at the study endpoints, the far-hand tail of the Kaplan–Meier curve should be interpreted with caution until confirmed by a larger cohort study. However, compared to other studies, we have described a relatively large sample size of pediatric KTx recipients spanning the past three decades. Our study may be useful in providing guidance to families with pediatric patients with ESRD.

In conclusion, improvements in immunosuppressive protocols have led to a better graft survival in pediatric KTx over the past three decades. In particular, avoiding early acute rejection after transplantation contributed to the improvement of graft survival rate after pediatric KTx.

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Conflict of interest

The authors have declared no conflicts of interests.

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Supporting information

Additional Supporting Information may be found in the online version of this article.

Table S1. Causes of graft loss (n = 400), by era

Table S2. Factors associated with graft loss using Cox regression model (n = 400)

Table S3. Causes of death (n = 377), by era

Table S4. Factors associated with patient death using Cox regression model (n = 377)

Figure legends

Fig. 1 Rejection-free rate after pediatric kidney transplantation by transplant era

Fig. 2 Graft survival after pediatric kidney transplantation by transplant era

Fig. 3 Patient survival after pediatric kidney transplantation

Fig. 4 Patient survival after pediatric kidney transplantation by transplant era

Table 1 Characteristics of the study population (n = 400), by era

Characteristic	All Eras (n = 400)	Era 1: 1975–1985 (n = 118)	Era 2: 1986–2001 (n = 161)	Era 3: 2002–2009 (n = 121)
Recipient characteristics				
Sex, male, n (%)	219 (54.8)	58 (49.2)	95 (59.0)	66 (54.5)
Age at KTx, year, median, (IQR)	9.7 (5.9–13.6)	11.5 (7.9–14.3)	9.6 (6.2–12.7)	7.8 (4.7–12.5)
Age group, year, n (%)				
1－3	45 (11.2)	7 (5.9)	16 (10.0)	22 (18.2)
4－6	87 (21.7)	18 (15.3)	34 (21.1)	35 (28.9)
7－10	101 (25.3)	29 (24.6)	49 (30.4)	23 (19.0)
11－14	106 (26.5)	41 (34.7)	42 (26.1)	23 (19.0)
15－18	61 (15.3)	23 (19.5)	20 (12.4)	18 (14.9)
Body weight at KTx, kg, median, (IQR)	20.6 (14.3–32.2)	26.1 (16.9–36.4)	20.0 (14.0–28.0)	17.0 (13.1–32.6)
Transplants, n				
First / second / third	375 / 22 / 3	105 / 10 /3	154 / 7 / 0	116 / 5 / 0
Pre-transplant dialysis, n (%)				
Peritoneal dialysis	239 (59.8)	26 (22.0)	117 (72.7)	96 (79.3)
Hemodialysis	131 (32.7)	89 (75.5)	38 (23.6)	4 (3.3)
No dialysis	30 (7.5)	3 (2.5)	6 (3.7)	21 (17.4)
Duration of dialysis, month, median, (IQR)	22.3 (11.7–42.4)	11.9 (5.9–18.9)	23.7 (13.8–42.1)	39.6 (23.7–52.2)
Duration of follow-up, year, median, (IQR)	15.3 (10.2–22.8)	20.3 (12.7–32.1)	18.6 (15.3–24.7)	10.2 (8.3–12.1)
Transplant variables				
HLA-mismatches, mean±SD	2.8±0.6	3.0±0.4	2.6±0.7	2.6±0.8
ABO-incompatible, n (%)	31 (7.8)	0 (0)	20 (12.4)	11 (9.1)

Cold ischemia time, minute, median, (IQR)	46 (38–256)	51 (48–191)	41 (35–251)	48 (42–62)
Delayed graft function, n (%)	26 (6.5)	14 (11.9)	5 (3.1)	7 (5.8)
Donor characteristics				
Donor age, year, median, (IQR)	39.6 (35.0–44.8)	38.0 (34.0–43.8)	39.0 (35.0–43.8)	41.8 (36.1–46.3)
Donor sex, male, n (%)	163 (40.8)	48 (40.7)	62 (38.5)	53 (43.8)
Living related donor, n (%)	364 (91.0)	101 (85.6)	156 (96.9)	107 (88.4)

KTx, kidney transplantation; IQR, interquartile range; HLA, human leukocyte antigen

Table 2 Primary renal diseases of recipients (n = 377), by era

Cause of renal failure, n (%)	All Eras (n = 377)	Era 1: 1975–1985 (n = 107)	Era 2: 1986–2001 (n = 154)	Era 3: 2002–2009 (n = 116)
CAKUT	154 (40.9)	35 (32.7)	70 (45.5)	49 (42.2)
Glomerulonephritis	100 (26.5)	44 (41.1)	25 (16.2)	31 (26.7)
FSGS	46 (12.2)	14 (13.1)	23 (14.9)	9 (7.9)
Hereditary nephropathy	35 (9.3)	6 (5.7)	22 (14.3)	7 (6.0)
Cystic kidney disease	18 (4.8)	1 (0.9)	5 (3.3)	12 (10.3)
HUS	13 (3.4)	5 (4.7)	6 (3.9)	2 (1.7)
Ischemic renal failure	9 (2.4)	1 (0.9)	3 (1.9)	5 (4.3)
Unknown	2 (0.5)	1 (0.9)	0 (0)	1 (0.9)

CAKUT, congenital anomalies of the kidney and urinary tract; FSGS, focal segmental glomerulosclerosis; HUS, hemolytic uremic syndrome
Glomerulonephritis (GN) includes IgA nephropathy, membrano-proliferative GN, membranous nephropathy,crescentic GN, and other types of GN. Hereditary nephropathy includes Alport's syndrome, congenital nephrotic syndrome, and other specified types. Cystic kidney disease includes polycystic kidney disease, nephronophthisis, and other specified types.

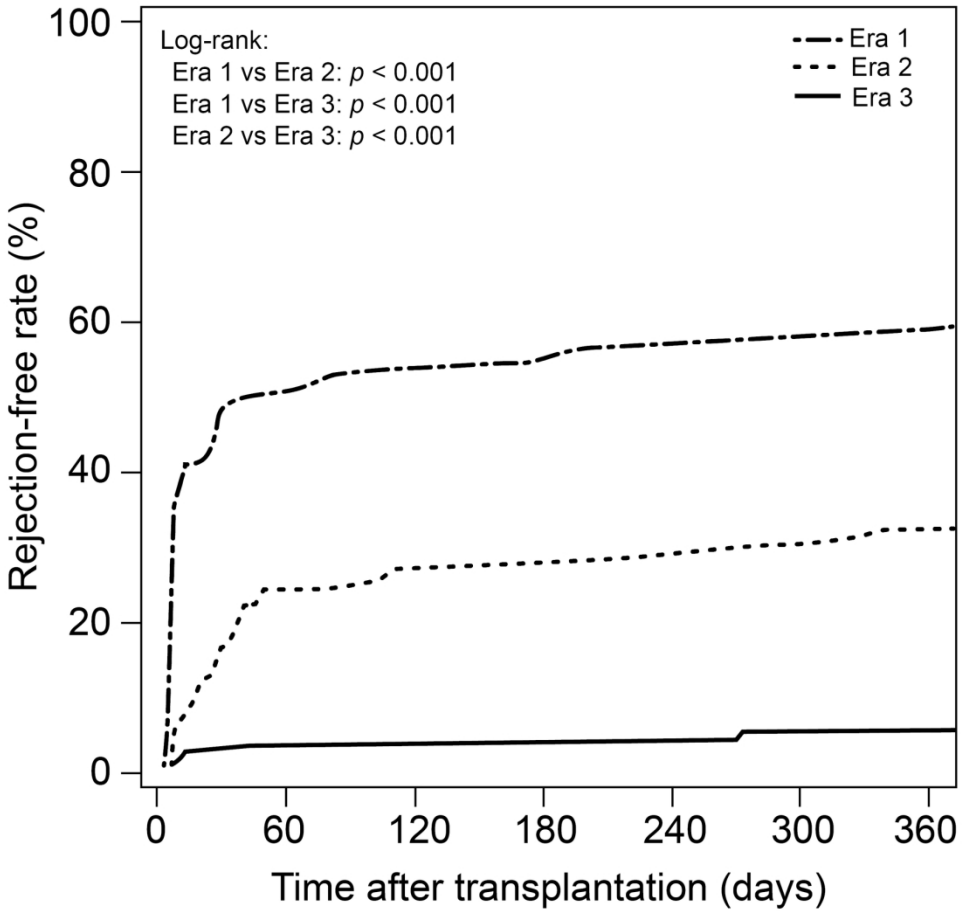
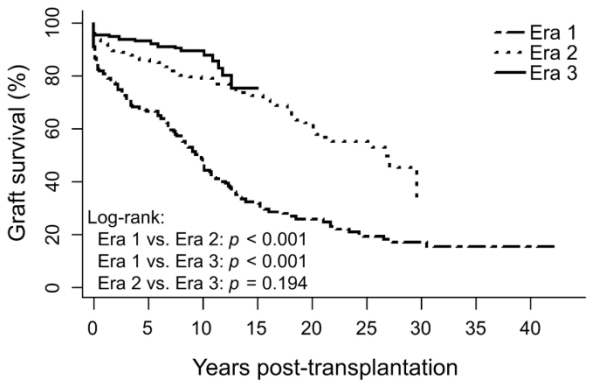


Fig. 1 Rejection-free rate after pediatric kidney transplantation by transplant era

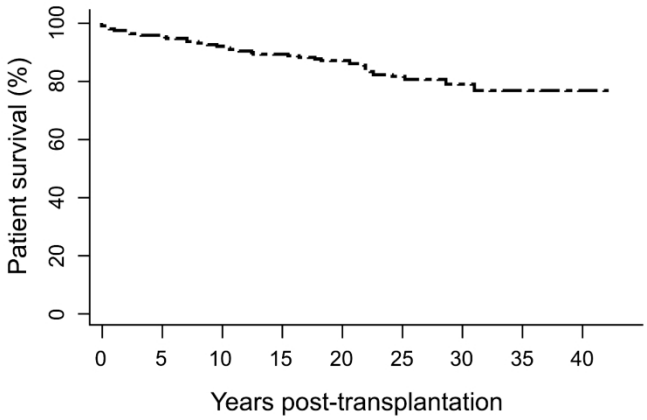
81x77mm (600 x 600 DPI)



	Baseline	5 years	10 years	15 years	20 years	25 years	30 years	35 years	40 years
Number of patients at risk									
Era 1	118	78	55	35	23	15	11	6	2
Era 2	161	137	121	98	46	27	3		
Era 3	121	111	59	1					
Survival (%)									
Era 1	100	66	47	31	25	19	17	15	15
Era 2	100	86	79	72	62	55	34		
Era 3	100	93	89	75					

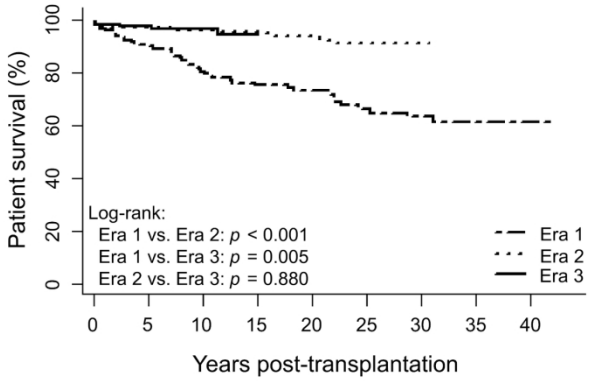
Fig. 2 Graft survival after pediatric kidney transplantation by transplant era

172x119mm (300 x 300 DPI)



Follow-up	Baseline	5 years	10 years	15 years	20 years	25 years	30 years	35 years	40 years
Number at risk	377	359	239	197	122	76	39	17	3
Survival (%)	100	96	93	90	88	82	81	78	78
(95% CI)		(94-98)	(90-96)	(87-93)	(84-92)	(77-88)	(75-87)	(72-86)	(72-86)

Fig. 3 Patient survival after pediatric kidney transplantation



	Baseline	5 years	10 years	15 years	20 years	25 years	30 years	35 years	40 years
Number of patients at risk									
Era 1	107	100	91	78	57	42	36	17	3
Era 2	154	147	140	119	65	34	3		
Era 3	116	112	62	1					
Survival (%)									
Era 1	100	94	85	79	77	69	68	66	66
Era 2	100	97	96	95	94	91	91		
Era 3	100	97	97	94					

Fig. 4 Patient survival after pediatric kidney transplantation by transplant era

172x119mm (300 x 300 DPI)

Table S1 Causes of graft loss (n = 400), by era

Cause of graft loss	All Eras (n = 400)	Era 1: 1975−1985 (n = 118)	Era 2: 1986−2001 (n = 161)	Era 3: 2002−2009 (n = 121)
< 1 year, n (%)				
Acute rejection	23 (52.3)	17 (68.0)	6 (46.2)	0 (0)
Death with functioning graft	7 (15.9)	3 (12.0)	3 (23.1)	1 (16.7)
Vascular complications	6 (13.6)	2 (8.0)	0 (0)	4 (66.6)
Primary nonfunction	4 (9.1)	2 (8.0)	2 (15.3)	0 (0)
Recurrent of primary disease	2 (4.5)	0 (0)	1 (7.7)	1 (16.7)
Chronic allograft nephropathy	1 (2.3)	1 (4.0)	0 (0)	0 (0)
Nonadherence	1 (2.3)	0 (0)	1 (7.7)	0 (0)
Total	44 (100.0)	25 (100.0)	13 (100.0)	6 (100.0)
1−10 years, n (%)				
Chronic allograft nephropathy	46 (69.7)	29 (76.3)	15 (71.4)	2 (28.6)
Death with functioning graft	11 (16.8)	8 (21.1)	1 (4.8)	2 (28.6)
Recurrence of primary disease	3 (4.5)	1 (2.6)	2 (9.5)	0 (0)
Acute rejection	3 (4.5)	0 (0)	1 (4.8)	2 (28.6)
Nonadherence	2 (3.0)	0 (0)	2 (9.5)	0 (0)
Vascular complications	1 (1.5)	0 (0)	0 (0)	1 (14.2)
Total	66 (100.0)	38 (100.0)	21 (100.0)	7 (100.0)
> 10 years, n (%)				
Chronic allograft nephropathy	56 (84.8)	26 (81.3)	25 (86.2)	5 (100.0)
Death with functioning graft	8 (12.1)	5 (15.6)	3 (10.3)	0 (0)
Recurrence of primary disease	2 (3.1)	1 (3.1)	1 (3.5)	0 (0)
Total	66 (100.0)	32 (100.0)	29 (100.0)	5 (100.0)

Table S2 Factors associated with graft loss using Cox regression model (n = 400)

Variable	Univariate analysis				Multivariate analysis			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value
Recipient sex (male vs. female)	0.754	0.561	1.013	0.061				
Recipient age								
1–3	0.700	0.377	1.301	0.260				
4–6	0.937	0.596	1.472	0.777				
7–10	Reference							
11–14	1.157	0.777	1.722	0.472				
15–18	1.147	0.724	1.819	0.559				
Primary disease								
CAKUT	Reference							
Glomerulonephritis	1.409	0.982	2.022	0.063				
FSGS	1.383	0.871	2.197	0.169				
Hereditary nephropathy	0.588	0.302	1.146	0.119				
Cystic kidney disease	0.815	0.327	2.028	0.660				
HUS	2.675	1.409	5.080	0.003				
Ischemic renal failure	1.051	0.382	2.889	0.923				
Body weight at KTx (<15 kg vs. ≥15 kg)	0.801	0.562	1.142	0.221				
Duration of dialysis (per month)	0.998	0.999	1.000	0.122				
Transplants (Primary vs. Re-transplant)	2.361	1.430	3.897	<0.001				
HLA mismatches number	1.057	0.875	1.277	0.566				
ABO compatibility (incompatible vs. compatible)	0.431	0.202	0.918	0.029				
Cold ischemia time (per minute)	1.002	1.001	1.002	<0.001	1.002	1.001	1.003	<0.001
Delayed graft function (Yes vs. No)	2.978	1.883	4.710	<0.001				
AR (number of times)	1.179	1.043	1.331	0.008	1.314	1.147	1.505	<0.001
Donor type (DD vs. LRD)	2.619	1.698	4.038	<0.001				
Donor sex (male vs. female)	0.615	0.449	0.843	0.002	0.478	0.337	0.678	<0.001
Donor age (≥50 years vs. <50 years)	1.471	0.891	2.437	0.131				
Transplant era								
Era 1 (1975–1985)	Reference							

Era 2 (1986–2001)	0.363	0.263	0.501	<0.001	0.364	0.256	0.517	<0.001
Era 3 (2002–2009)	0.223	0.134	0.372	<0.001	0.272	0.161	0.458	<0.001

CAKUT, congenital anomalies of the kidney and urinary tract; FSGS, focal segmental glomerulosclerosis; HUS, hemolytic uremic syndrome; KTx, kidney transplantation; AR, acute rejection; DD, deceased donor; LRD, living-related donor

Table S3 Causes of death (n = 377), by era

Cause of death	All Eras (n = 377)	Era 1: 1975−1985 (n = 107)	Era 2: 1986−2001 (n = 154)	Era 3: 2002−2009 (n = 116)
< 1 year, n (%)				
Infection disease 1 psoas abscess and sepsis, 1 measles	2 (20.0)	1 (25.0)	1 (25.0)	0 (0)
Heart disease 2 hyperkalemic cardiac arrest, 2 heart failure	4 (40.0)	2 (50.0)	1 (25.0)	1 (50.0)
Cerebrovascular disease 1 cerebral hemorrhage	1 (10.0)	1 (25.0)	0 (0)	0 (0)
Respiratory disease 1 acute respiratory distress syndrome	1 (10.0)	0 (0)	1 (25.0)	0 (0)
Malignant neoplasm 1 gastrointestinal PTLD	1 (10.0)	0 (0)	1 (25.0)	0 (0)
Others 1 intra-abdominal bleeding	1 (10.0)	0 (0)	0 (0)	1 (50.0)
Total	10 (100.0)	4 (100.0)	4 (100.0)	2 (100.0)
1−10 years, n (%)				
Infection disease 2 pneumonia, 1 measles, 1 viral infection, 1 bacterial sepsis	5 (33.4)	5 (45.4)	0 (0)	0 (0)
Cerebrovascular disease 2 cerebral hemorrhage	2 (13.3)	2 (18.2)	0 (0)	0 (0)
Respiratory disease 1 pulmonary hypertension, 1 pulmonary edema, 1 aspiration by status epilepticus	3 (20.0)	2 (18.2)	0 (0)	1 (50.0)
Gastrointestinal disease 1 peritonitis, 1 strangulated ileus	2 (13.3)	1 (9.1)	1 (50.0)	0 (0)
Malignant neoplasm 1 PTLD	1 (6.7)	0 (0)	0 (0)	1 (50.0)
Others 1 liver failure, 1 traffic accident	2 (13.3)	1 (9.1)	1 (50.0)	0 (0)
Total	15 (100.0)	11 (100.0)	2 (100.0)	2 (100.0)
> 10 years, n (%)				
Infection disease 3 bacterial sepsis, 1 pneumonia, 1 necrotic cholecystitis	5 (22.7)	4 (25.0)	1 (20.0)	0 (0)
Heart disease 2 heart failure, 1 acute aortic dissection	3 (13.6)	2 (12.5)	0 (0)	1 (100.0)
Respiratory disease 1 idiopathic pulmonary hemorrhage	1 (4.6)	0 (0)	1 (20.0)	0 (0)
Gastrointestinal disease 2 bowel perforation, 1 encapsulating peritoneal sclerosis	3 (13.6)	2 (12.5)	1 (20.0)	0 (0)
Malignant neoplasm 1 renal tumor in transplanted kidney, 1 malignant schwannoma, 1 liver cancer	3 (13.6)	3 (18.8)	0 (0)	0 (0)
Others 4 liver failure, 3 sudden unknown	7 (31.9)	5 (31.2)	2 (40.0)	0 (0)
Total	22 (100.0)	16 (100.0)	5 (100.0)	1 (100.0)

Table S4 Factors associated with patient death using Cox regression model (n = 377)

Variable	Univariate analysis				Multivariate analysis			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value
Recipient sex (male vs. female)	1.077	0.603	1.924	0.803				
Recipient age								
1－3	0.489	0.140	1.701	0.260				
4－6	0.915	0.406	2.062	0.624				
7－10	Reference							
11－14	0.798	0.375	1.702	0.560				
15－18	0.796	0.321	1.977	0.624				
Primary disease								
CAKUT	Reference							
Glomerulonephritis	1.774	0.893	3.527	0.102				
FSGS	1.490	0.608	3.656	0.383				
Hereditary nephropathy	0.783	0.226	2.704	0.698				
Cystic kidney disease	0.685	0.090	5.197	0.715				
HUS	2.134	0.615	7.408	0.233				
Ischemic renal failure	0.000	0.000	Inf	0.996				
Body weight at KTx (<15 kg vs. ≥15 kg)	0.814	0.414	1.599	0.550				
Duration of dialysis (per month)	1.000	0.999	1.001	0.123				
Transplants (Primary vs. Re-transplant)	20.13	4.726	85.75	<0.001	6.858	1.274	36.92	0.025
HLA mismatches number	0.819	0.580	1.155	0.255				
ABO compatibility (incompatible vs. compatible)	0.834	0.259	2.691	0.762				
Cold ischemia time (per minute)	1.003	1.001	1.004	<0.001	1.003	1.000	1.005	0.023
Delayed graft function (Yes vs. No)	3.694	1.562	8.738	0.003				
AR (number of times)	0.811	0.583	1.128	0.213				
Donor type (DD vs. LRD)	2.777	1.177	6.551	0.020				
Donor sex (male vs. female)	0.869	0.475	1.59	0.649				
Donor age (≥50 years vs. <50 years)	2.053	0.869	4.852	0.101				
Transplant era								
Era 1 (1975–1985)	Reference							
Era 2 (1986–2001)	0.268	0.134	0.535	<0.001				
Era 3 (2002–2009)	0.275	0.104	0.732	0.010				

CAKUT, congenital anomalies of the kidney and urinary tract; FSGS, focal segmental glomerulosclerosis; HUS, hemolytic uremic syndrome; KTx, kidney transplantation; AR, acute rejection; DD, deceased donor; LRD, living-related donor