

Original Article: Clinical Investigation**Long-term outcomes of pediatric kidney transplantation:
A single-center experience over the past 34 years in Japan**

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Abbreviations & Acronyms

ABO-cKTx = ABO-compatible KTx
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
CNI = calcineurin inhibitor
CPM = cyclophosphamide
CsA = cyclosporine A
DD = deceased donor
DGF = delayed graft function
DSG = deoxyspergualine
DWF = death with a functioning graft
ESRD = end-stage renal disease
FSGS = focal segmental glomerulosclerosis
HD = hemodialysis
HLA = human leukocyte antigen
HR = hazard ratio
HUS = hemolytic uremic syndrome
IQR = interquartile range
i.v. = 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
Tac = tacrolimus
TMCMC = Tokyo Metropolitan Children's Medical Center
VIF = variance inflation factor

Objectives: To evaluate long-term outcomes and risk factors for graft loss in pediatric kidney transplantation over a 30-year period.

Methods: We retrospectively assessed 400 consecutive kidney transplants carried out in 377 children during 1975–2009. Patients were stratified according to the immunosuppressive regimen (era 1: methylprednisolone and azathioprine; era 2: calcineurin inhibitor-based therapy, including methylprednisolone and azathioprine or mizoribine; era 3: basiliximab induction therapy, including calcineurin inhibitors, methylprednisolone and mycophenolate mofetil).

Results: The median age and bodyweight at transplantation were 9.7 years and 20.6 kg, respectively. In total, 364 (91.0%) children received a living related donor transplantation. The acute rejection rate within 1 year post-transplant decreased significantly from 61.0% in era 1 to 14.5% in era 3 ($P < 0.001$). For transplant eras 1–3, 1-year graft survival was 81%, 93% and 95%; 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 1.385, 95% confidence interval 1.251–1.603), acute rejection (hazard ratio 1.682, 95% confidence interval 1.547–3.842), re-transplant (hazard ratio 2.680, 95% confidence interval 1.759–3.982) and donor type (hazard ratio 2.957, 95% confidence interval 1.754–4.691) as independent risk factors for graft loss at 10 years post-transplant.

Conclusions: The progress of immunosuppressive therapy has led to a low incidence of acute rejection and a high graft survival rate across 30 years of pediatric transplantation.

Key words: ABO-incompatible, graft survival, kidney transplantation, mortality, pediatric.

Introduction

ESRD is a rare and severe condition in children. Approximately five to 10 children per million in the age-related population are initiated on RRT yearly, and the mortality rate in children with ESRD might be 30-fold 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 infection monitoring and management.^{3,4} Furthermore, 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 be managed 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}

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

Methods

Study design and patient population

This single-center retrospective study was carried out at the TCMC. We reviewed the medical charts of all consecutive 400 KTx carried out in patients aged ≤ 18 years at the Tokyo Metropolitan Kiyose Children's Hospital (the predecessor of TCMC) between January 1975 and December 2009. The majority of transplant recipients were transferred to the TCMC 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, and 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 TCMC (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 was tapered to a maintenance dose of 0.2–0.25 mg/kg/day for 4 months after KTx. AZA was administered at a maintenance dose of 1.5 mg/kg/day continuously. MZR was maintained for at least 4 weeks postoperatively, then tapered to a maintenance dose of 3 mg/kg/day.¹⁰

Era 2: 1986 to 2001

CNI were utilized in era 2. CsA was introduced in June 1986, and Tac was introduced in February 1997. 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 4 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. The 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 at 1 year post-transplantation. Oral Tac was started at 0.3 mg/kg/day on the day before KTx, and i.v. Tac was administered until day 5 after KTx. The target trough level of TAC was 15–20 ng/mL during the first 2 months, 10–20 ng/mL by month 4 and 7–10 ng/mL at 1 year after transplantation. 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 the first postoperative month, 3200–3500 ng/mL by the fourth month and 2500–2800 ng/mL at 1 year. Tac was started orally at 0.3 mg/kg/day on the day before KTx, and was then administered i.v. until 5 days after KTx. The target trough levels were 10–13 ng/mL during the first month, 7–10 ng/mL by the fourth month and 5–7 ng/mL at 1 year after KTx. The MPL dose was rapidly reduced to a maintenance dose of 4 mg on alternate days 3 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.

ABO-incompatible kidney transplantation: ABO-incKTx was carried out as of September 1989 at Tokyo Metropolitan Kiyose Children's Hospital. All transplant recipients underwent plasmapheresis three to four times to remove anti-A/B antibodies on days 4, 2 and 1 before KTx. The aim was to reduce the anti-A/B antibody titer to $<1:8$ before surgery. Before 2000, the immunosuppressive protocol consisted of CsA, MPL, CPM and ALG. MPL was started at 10 mg/m²/day orally on the day of KTx, and a single dose of 20 mg/kg MPL was administered i.v. intraoperatively. Thereafter, MPL was increased to 40 mg/m²/day and tapered from the day after transplantation. CPM was used to suppress anti-A/B antibody production for 10 days before transplantation, and was then switched to AZA at 1-month post-KTx. After 2002, MMF was used instead of CPM; DSG or BXM was used for induction therapy. The target trough level of CsA was 200–300 ng/mL during the first 2 months, 150–200 ng/mL for the next 2 months and 100–120 ng/mL thereafter. All ABO-incKTx recipients underwent splenectomy at the time of KTx, and rituximab was not used.

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 AR diagnosis was based on the findings of a kidney allograft biopsy using the Banff classification. However, anti-HLA antibodies were not investigated during AR diagnosis in this study. AR was treated with bolus i.v. 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 1 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 \pm SD and median and range or IQR, depending on the normality of the distribution. Categorical data were analyzed using the χ^2 -test or Fisher's exact test, and continuous data were analyzed using the Mann–Whitney *U*-test. 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 carried out 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. Statistical analyses were carried out using SPSS software (version 22.0; SPSS, Chicago, IL, 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 carried out in 377 patients,

and 23 patients (6.1%) underwent re-transplantation. The median age was 9.7 years (range 1.6–18.8 years), and the median bodyweight was 20.6 kg (range 7.4–70.0 kg) at KTx. The median duration of follow up was 15.3 years (range 0.0–42.2 years), and the median age of the survivors at last follow up was 26.3 years (range 8.7–57.6 years).

A total of 30 recipients (7.5%) underwent preemptive 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 months). The duration of dialysis increased from era 1 to era 3. A total of 364 donors were LRD (91.0%), and 36 were DD (9%). The median age of the donors was 39 years (IQR 35–44 years) for LRD, and 33 years (IQR 18–46 years) for DD. LRD had a significantly lower CIT than DD (median 44 vs 406 min, $P < 0.0001$).

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.

Table 1 Characteristics of the study population by era

Characteristic	All eras (<i>n</i> = 400)	Era 1: 1975–1985 (<i>n</i> = 118)	Era 2: 1986–2001 (<i>n</i> = 161)	Era 3: 2002–2009 (<i>n</i> = 121)	<i>P</i> -value
Recipient characteristics					
Male, <i>n</i> (%)	219 (54.8)	58 (49.2)	95 (59.0)	66 (54.5)	0.268
Median age at KTx, years (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)	<0.001
Age group, years, <i>n</i> (%)					
1–3	45 (11.2)	7 (5.9)	16 (10.0)	22 (18.2)	0.011
4–6	87 (21.7)	18 (15.3)	34 (21.1)	35 (28.9)	0.037
7–10	101 (25.3)	29 (24.6)	49 (30.4)	23 (19.0)	0.091
11–14	106 (26.5)	41 (34.7)	42 (26.1)	23 (19.0)	0.023
15–18	61 (15.3)	23 (19.5)	20 (12.4)	18 (14.9)	0.270
Median bodyweight at KTx, kg (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)	0.002
Transplants, <i>n</i> (%)					
Primary/re-transplant	375 (93.8)/25 (6.2)	105 (89.0)/13 (11.0)	154 (95.7)/7 (4.3)	116 (95.9)/5 (4.1)	0.050
Pre-transplant dialysis, <i>n</i> (%)					
Peritoneal dialysis	239 (59.8)	26 (22.0)	117 (72.7)	96 (79.3)	<0.001
Hemodialysis	131 (32.7)	89 (75.5)	38 (23.6)	4 (3.3)	<0.001
No dialysis	30 (7.5)	3 (2.5)	6 (3.7)	21 (17.4)	<0.001
Median duration of dialysis, months (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)	<0.001
Median duration of follow up, years (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)	<0.001
Transplant variables					
HLA-mismatches (mean ± SD)	2.8 ± 0.6	3.0 ± 0.4	2.6 ± 0.7	2.6 ± 0.8	0.085
ABO-incompatible, <i>n</i> (%)	31 (7.8)	0 (0)	20 (12.4)	11 (9.1)	<0.001
Median cold ischemia time, min (IQR)	46 (38–256)	51 (48–191)	41 (35–251)	48 (42–62)	<0.001
Delayed graft function, <i>n</i> (%)	26 (6.5)	14 (11.9)	5 (3.1)	7 (5.8)	0.014
Immunosuppressants, <i>n</i> (%)					
Cyclosporin A	191 (47.8)	0 (0)	133 (82.6)	58 (47.9)	<0.001
Tacrolimus	91 (22.8)	0 (0)	28 (17.4)	63 (52.1)	<0.001
Azathioprine	132 (33.0)	52 (44.1)	80 (49.7)	0 (0)	<0.001
Mizoribine	137 (34.3)	46 (38.9)	73 (45.3)	18 (14.9)	<0.001
Azathioprine and mizoribine	28 (7.0)	20 (17.0)	8 (5.0)	0 (0)	<0.001
Mycophenolate mofetil	103 (25.8)	0 (0)	0 (0)	103 (85.1)	<0.001
Basiliximab	107 (26.8)	0 (0)	0 (0)	107 (88.4)	<0.001
Donor characteristics					
Median donor age, years (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)	0.049
Donor sex, male, <i>n</i> (%)	163 (40.8)	48 (40.7)	62 (38.5)	53 (43.8)	0.683
Living related donor, <i>n</i> (%)	364 (91.0)	101 (85.6)	156 (96.9)	107 (88.4)	0.001

Table 2 Primary renal diseases of recipients 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)	P-value
CAKUT	154 (40.9)	35 (32.7)	70 (45.5)	49 (42.2)	0.112
Glomerulonephritis	100 (26.5)	44 (41.1)	25 (16.2)	31 (26.7)	<0.001
FSGS	46 (12.2)	14 (13.1)	23 (14.9)	9 (7.9)	0.185
Hereditary nephropathy	35 (9.3)	6 (5.7)	22 (14.3)	7 (6.0)	0.027
Cystic kidney disease	18 (4.8)	1 (0.9)	5 (3.3)	12 (10.3)	0.003
HUS	13 (3.4)	5 (4.7)	6 (3.9)	2 (1.7)	0.458
Ischemic renal failure	9 (2.4)	1 (0.9)	3 (1.9)	5 (4.3)	0.239
Unknown	2 (0.5)	1 (0.9)	0 (0)	1 (0.9)	0.515

Glomerulonephritis includes immunoglobulin A nephropathy, membrano-proliferative glomerulonephritis, membranous nephropathy, crescentic glomerulonephritis and other types of glomerulonephritis. 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.

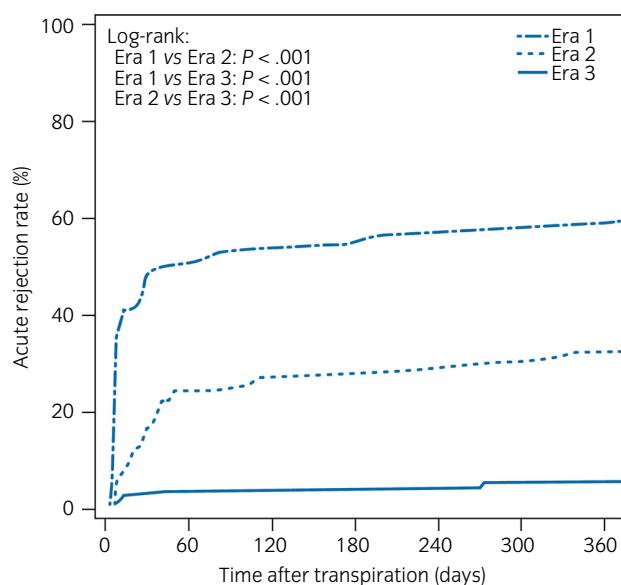


Fig. 1 Acute rejection rate after pediatric kidney transplantation by transplant era.

Acute rejection

The incidence of AR episodes was decreased and delayed over time. In era 1, 61.0% of patients showed AR. However, this proportion was reduced to 41.6% in era 2 and 14.5% in era 3 (log-rank $P < 0.001$, Wilcoxon $P < 0.001$, respectively; Fig. 1). The median time to AR episodes was 7 days (IQR 6–28 days) in era 1 and 40 days (IQR 19–334 days) in era 2. From era 3, the median time to AR episodes increased to 705 days (IQR 28–2544 days).

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 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 each transplant era is shown in Figure 2. The graft survival rate improved in eras 2 and 3 (log-rank $P < 0.001$, Wilcoxon $P < 0.001$, respectively) compared with era 1. However, these rates did not differ significantly between eras 2 and 3 (log-rank $P = 0.194$, 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 $P < 0.001$; Wilcoxon $P = 0.018$, respectively). In 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 patients, 176 experienced failed graft function during the study period. The causes of graft loss according to each period are shown in Table S1. 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 era 1. In era 3, the most common cause of graft loss within the first year post-KTx was vascular complications; three recipients had vascular thrombosis.

Recipient and donor risk factors were analyzed for graft survival at 10 years post-transplant. The results of the univariate and multivariate analyses are shown in Table S2. Univariate analysis showed that HUS, re-transplant, CIT, DGF, AR, donor type and transplant era were significant predictors of survival. The factors with $P < 0.1$ included in the multivariate analysis were re-transplant, CIT, AR, donor type and transplant era, all of which were found to be significant predictors of graft survival at 10 years post-transplant.

Patient survival

Overall patient survival is shown in Figure 3. Patient survival improved in eras 2 and 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 in 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%; seven patients). Causes of death stratified by transplant era are detailed in Table S3. During follow up, the median age at death was 23.0 years (range 2.1–45.4 years). The median time between KTx and death was 8.4 years (range 1 day to 31.0 years). A total of 47 of 377 patients died; 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 1–3 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 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 Table S4. Univariate analysis showed that re-transplant, 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 a 34-year period. The incidence of AR episodes decreased and was delayed as immunosuppressive therapy evolved; the 10-year graft survival rate in eras 1–3 were 47, 79 and 89%, respectively; graft half-life exceeded 25 years after the introduction of CNIs; and after pediatric KTx, patients had a 30-year survival rate exceeding 80%.

Short- and medium-term patient survival after pediatric KTx has been found to be consistently $>90\%$ 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 United States Renal Data System showed that the 20-year survival rate of patients aged <21 years who received their transplant between 1983 and 2006 was 66.4%.¹¹ Data from single-center and national cohorts showed that the 15- to 20-year patient survival after pediatric KTx was 72–91%,^{6–9} which is in line with the data from a previous study showing patient survival exceeding

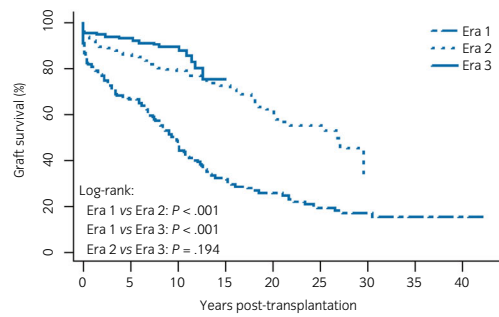
80% at 30 years post-KTx, as calculated using the Kaplan–Meier method. In previous studies as well as in our own, the major causes of death were infection, cardiovascular disease and malignancies.^{6,11,12}

The graft survival rate has markedly improved over the past decades.^{5,12,13} The present study also showed an improvement in short-term graft survival across the three transplantation eras. Long-term graft survival was 45–72% at 10 years, 35–59% at 15 years and 30–40% at 20 years in previous reports.^{6–9} The data from the present 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. Consistently with previous reports, a substantial increase in the graft survival rate was observed during the last period of the present 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 the present study; indeed, graft loss by CAN exceeded 80% at 10 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 the present study, the independent predictors of graft survival were transplant era, donor sex, CIT and AR.

With the progress of immunosuppressive drugs, AR became less frequent due to the introduction of CNIs and BXM, which resulted in better graft survival in the present study. Two multicenter prospective studies have reported the lack of association between induction agent use 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}

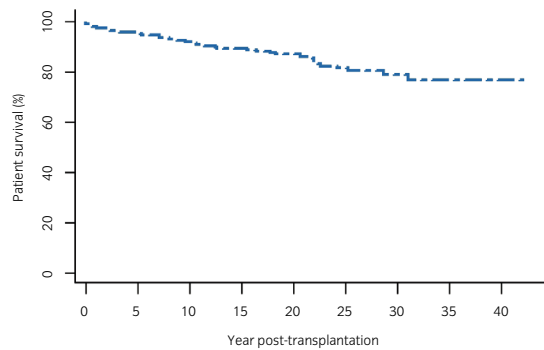
The retrospective nature of our analysis and the relatively small number of events are important limitations of the present study. In our cohort, there was no systematic record of data on kidney function or social outcomes after KTx. Furthermore, the sample number decreased with time, which means the far-hand tail of the Kaplan–Meier curve should be interpreted with caution until confirmed by a larger cohort study. However, compared with other studies, we have described a relatively large sample size of pediatric KTx recipients spanning the past three decades. The present study might 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 patients over the past three decades. In particular, avoiding early acute rejection after transplantation contributed to the improvement of graft survival rate after pediatric KTx. We should endeavor to reduce perioperative complications and to suppress the progression of chronic tissue damage to further improve outcomes.



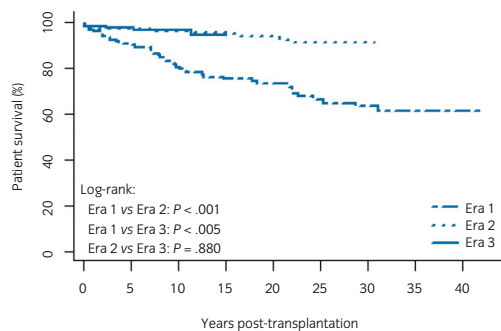
	Baseline	5 years	10 years	15 years	20 years	25 years	30 years	35 years	40 years
No. of patients at risk									
Era 1	118	78	55	35	23	15	11	6	2
Era 2	161	137	121	98	46	27	3		
Era 3	121	111	59	1					
Survival (%)									
Era 1	100	66	47	31	25	19	17	15	15
Era 2	100	86	79	72	62	55	34		
Era 3	100	93	89	75					

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



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
No. 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.

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Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

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

Table S2. Factors associated with graft loss at 10 years post-transplant using a 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 ($n = 377$).