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ORIGINAL ARTICLE

Long-term critical issues in pediatric renal transplant recipients: a single-center experience

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Summary

Data on long-term outcomes after pediatric renal transplantation (Tx) are still limited. We report on a 20-year single-center experience. Medical charts of all consecutive pediatric Tx performed between 1987 and 2007 were reviewed. Data of patients who had been transferred to adult units were extracted from the French databases of renal replacement therapies. Outcomes were assessed using Kaplan–Meier and Cox models. Two hundred forty Tx were performed in 219 children (24.1% pre-emptive and 17.5% living related donor Tx). Median age at Tx was 11.1 years and median follow-up was 10.4 years. Patient survival was 94%, 92%, and 91% at 5, 10, and 15 years post-Tx, respectively. Overall, transplant survival was 92%, 82%, 72%, and 59% at 1, 5, 10, and 15 years post-Tx, respectively. The expected death-censored graft half-life was 20 years. Sixteen patients developed malignancies during follow-up. Median height at 18 years of age was 166 cm in boys and 152 cm in girls with 68% of patients being in the normal range. The proportion of socially disadvantaged young people was higher than in general population. Excellent long-term outcomes can be achieved in pediatric renal Tx, but specific problems such as malignancies, growth, and social outcome remain challenging.

Introduction

End-stage renal disease (ESRD) is a rare condition in children. Approximately, nine children per million age-related population start renal replacement therapy (RRT) each year worldwide [1]. Based on information from national or international registries that have accumulated data, many lessons have been learned about pediatric ESRD. Renal transplantation (Tx) is now widely recognized as the treatment of choice for children with ESRD according to both survival and quality of life [2]. Over the past two decades, the number of adults who started RRT during childhood has been increasing [3]. The life expectancy benefit over chronic dialysis for transplanted young adults who began RRT during childhood may be as much as 25 years [3]. A report from the United States Renal Data System (USRDS)

has demonstrated that transplanted children have a survival benefit when compared with those on the waiting list that is more pronounced than what is found in adults [4]. In addition, a functioning renal transplant enables children to attend school and improves cognitive development and linear growth particularly in younger children [5–8]. However, data on outcomes over 20 years after renal Tx in childhood are still limited to a few reports [9–11]. Registries focusing on pediatric Tx usually do not provide sufficient follow-up to evaluate what these children have become who have reached adulthood. Such information on long-term mortality, graft survival, malignancies, final height, or psycho-social adjustment is of crucial importance for clinicians to improve management, and to provide reliable prognosis and counseling to patients and their families.

Although large databases are mandatory to perform adequately powered studies, single-center studies may obtain more accurate and detailed information about pediatric Tx. Moreover, the combination of pediatric and adult registries to follow children with ESRD further into adulthood is notoriously difficult. Conversely, a single-center study may offer the opportunity to provide longitudinal data on the long-term consequences of Tx from the pediatric to the adult age. The objectives of this study were therefore to estimate the long-term incidence and the determinants of mortality, graft failure, and cancer, and to describe the final height and the social outcome in pediatric renal transplant recipients.

Methods

Study design and population

A single-center retrospective study was conducted at the University Hospital of Lyon. We reviewed the medical charts of all consecutive renal Tx performed between April 1987 and March 2007. Data from patients who had been transferred to adult units were extracted from the French registries of dialysis (REIN) and Tx (CRISTAL). Methods and quality controls of these two registries are well established and have been described elsewhere [12,13]. More information has been obtained from clinicians in charge of the patient care in other centers, and collected from families in some cases.

Immunosuppressive regimen

From 1987 to 2000, the immunosuppressive protocol consisted of anti-thymocyte globulins (ATG), predniso(lo)ne, azathioprine (AZA), and cyclosporine (CyA) in cases of *de novo* Tx. ATG was administered as induction therapy at a dose of 2 mg/kg/day during the first 10 days post-Tx. Prednisolone was started preoperatively at a single dose of 300 mg/m² followed by prednisone 60 mg/m²/day until day 14 post-Tx, and then was progressively reduced to 2.5 mg/m²/day after 12 months post-Tx. AZA was given preoperatively at a dose of 3 mg/kg, was changed to 2 mg/kg/day over the first 2 months, and then to 1 mg/kg/day thereafter. CyA was started orally as soon as serum creatinine fell below 100 μmol/l. The target CyA through blood level was 150–200 ng/ml during the first 6 months and 100–150 ng/ml thereafter. Immunosuppressive protocol changed since the year 2000. Prednisolone was then given preoperatively at a dose of 60 mg/m²; induction therapy consisted of basiliximab at days 0 and day 4; AZA was replaced by mycophenolate mofetil, administered preoperatively at a dose of 500 mg/m² and then 1200 mg/m²/day after Tx; and CyA was started within the first 48 h. Patients with a second or third Tx, and those with steroid resistant nephrotic syndrome, were managed on individual basis.

Data collection and clinical definitions

Information recorded for this study included recipient and donor characteristics, treatment, graft function, acute rejection episodes (ARE), anthropometric and social data, and main outcome events (death, graft failure, cancer, loss to follow-up). Renal function assessment was performed at 1-year post-Tx, and yearly thereafter. The glomerular filtration rate (GFR) was measured by the clearance of inulin as described elsewhere [14]. ARE were not systematically biopsy proven and were defined as an increase in baseline creatinine leading to specific treatment. Delayed graft function was defined by the need of dialysis post-Tx. Anthropometric parameters including height were recorded at the time of Tx and at each visit until transfer to adult unit at which the last available height was obtained. Final height was defined as growth velocity <1 cm per year after puberty has occurred. Growth parameters were plotted on growth charts using standard deviation score (SDS) adapted to gender and French standard measurements [15]. Graft failure was defined as a return to dialysis, re-Tx, or death. Identification of malignancy was made by biopsy of the affected organ. Social information and educational level were obtained by reviewing all available medical charts, and by interviews about current history.

Statistical analysis

Results were expressed as median and range or interquartile range (IQR) for continuous variables, and as percentages for categorical variables. Mortality rate and malignancy incidence rate were calculated. Unadjusted patient survival, graft, and death-censored graft survival rates were estimated using the Kaplan–Meier method. Graft half-lives were calculated as median half-lives, i.e. the intersection point of the survival curve

with the 50% threshold. The association between patient characteristics and the main outcomes was determined using Cox proportional hazard models. For patient and graft survival, variables tested in the univariable analyses included gender, age at Tx [<3 years, 3–12 years (reference group), 13–19 years], primary disease [congenital structural abnormality (reference group), hereditary nephropathy, glomerular disease, other], number of Tx (repeat Tx vs. first Tx), dialysis modality [HD, PD, pre-emptive Tx (reference group)] and duration (years), donor age (years), donor type [living related donor (LRD) vs. deceased donor], human leukocyte antigen (HLA) matching (5–6 vs. <5 A+B+DR mismatches), cold ischemia time (hours), delayed graft function (yes versus no). A second graft survival analysis was restricted to children who had more than 1 year of graft function. In addition to the previous variables, two additional variables were tested in univariables analyses: ARE within the first year post-Tx ($\geq$ 1 vs. 0) and measured GFR at 1 year post-Tx. Variables with P values ≤ 0.20 in the univariables analyses were entered in the full multivariable models. The subsequent multivariable modeling procedure was based on a stepwise backward selection. Variables with P values >0.05 were removed from the models unless they had a confounding effect on the remaining variables.

To assess for an era effect, we defined two 10-year Tx eras (1987–1996 and 1997–2007). Interaction terms between era and each of the variables included in the final multivariable model were investigated. When the interaction was found to be statistically significant ($P < 0.05$), the final model was stratified on the era.

The adequacy of each proportional hazard model was checked. Incidences and hazard ratios were reported with their 95% confidence interval (CI). Factors associated with final height (estimated by SDS at the time of transfer in adult unit) were assessed using a linear regression model. P values were adjusted for multiple testing corrections. All statistical analyses were carried out using SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA).

Results

Population characteristics

During the 20-year period, 240 renal Tx were performed in 219 children (127 boys) aged <20 years. The median age at Tx was 11.1 (range 0.6–19.9) years, three patients were aged between 18 and 20 at the time of Tx. There were 42 LRD Tx (17.5%) and 198 DD Tx. Of note, as a consequence of the kidney allocation rule in France where pediatric recipients are given national priority for kidneys from pediatric donors, almost all DD in this cohort were pediatric donors.

The charts of the patients were reviewed until 31 December 2007. Thus, the median duration of the follow-up was 10.4 (range 0.1–20.4) years and the median age of surviving patients at last follow-up was 20.8 (range 4.1–36.5) years. Among the survivors, 122 have been transferred into adult units. The main population characteristics are summarized in Table 1.

Patient survival

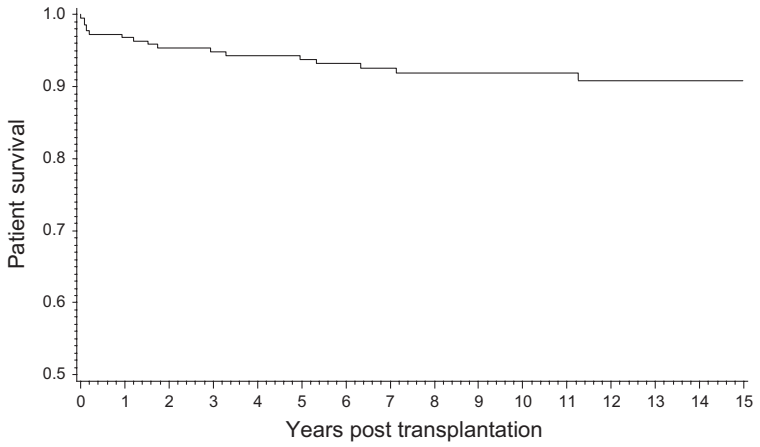
Seventeen of 219 patients died corresponding to a crude mortality rate of 0.74 per 100 patient-years (CI 0.46, 1.19). Patient survival was 97%, 94%, 92%, and 91%, at 1, 5, 10, and 15 years post-Tx, respectively (Fig. 1). The main causes of death were infections (41%) and malignancies (24%). Causes of deaths are detailed in Table 2. Patient survival in children <3 years of age was 88%, 84%, and 76% at 5, 10, and 15 years post-Tx. In univariable analysis, the risk of death was threefold higher in children <3 years at Tx. In multivariable analysis, mortality remained twice as high in the younger age group. No other variable was significantly associated with patient survival (supplementary Table S1).

Graft survival

A total of 79 grafts were lost including 12 deaths with a functioning graft. The causes of graft losses are shown in Table 2. Overall graft survival was 90%, 79%, 67%, and 55%, at 1, 5, 10, and 15 years post-Tx, respectively. Death-censored graft survival was 92%, 82%, 72%, and 59%, at 1,

Table 1. Characteristics of the study population.

Variable	
Male gender, *n* (%)	127 (58.0)
Caucasian origin, *n* (%)	170 (77.6)
Recipient age at Tx, median (IQR)	11.1 (5.4–14.4) years
Age, *n* (%)	
<3 years	26 (10.8)
3–12 years	124 (51.7)
$\geq$ 13 years	90 (37.5)
Primary disease, *n* (%)	
Congenital structural abnormality	78 (32.5)
Hereditary renal disease	73 (30.5)
Glomerular disease	50 (21.0)
Other	38 (16.0)
Dialysis modality prior to Tx, *n* (%)	
Hemodialysis	118 (49.2)
Peritoneal dialysis	64 (26.7)
No dialysis	58 (24.1)
Duration of dialysis, median (IQR)	8.1 (3.0–16.9) months
Living related donor Tx, *n* (%)	42 (17.5)
Donor age, median (IQR)	10.9 (5.7–18.9) years
Transplantation, *n* (%)	
Primary	211 (87.9)
Re-transplantation	29 (22.1)
Cold ischemia time, median (IQR)	16 (8–24) hours
Delayed graft function, *n* (%)	14 (5.8)
HLA mismatches, median number (IQR)	4 (2–5)



Follow-up	Baseline	5 years	10 years	15 years
N at risk	219	165	115	65
Survival	100	94 [CI 90, 97]	92 [88, 95]	91 [86, 95]

Figure 1 Patient survival after renal transplantation.

Table 2. Causes of death and graft loss after renal transplantation.

	n	%
Causes of death (*n* = 17)		
Infections (4 bacterial sepsis, 1 pneumonia, 1 fungal infection, 1 CMV infection)	7	41.2
Malignancies (PTLD, PTLD with cerebral and respiratory complications, Burkitt lymphoma with metabolic complications, B-cell lymphoma)	4	23.5
Neurological disorders (neurological complications of HUS, unexplained cerebral edema with hyponatremia)	2	11.8
Miscellaneous (2 unexplained sudden death, respiratory complications of Schimke immuno-osseous dysplasia, gas embolism after return on dialysis)	4	23.5
Causes of graft loss (*n* = 79)		
Chronic rejection	31	39.2
Vascular complications	10	12.7
Immunosuppression discontinued	8	10.1
Acute rejection	6	7.6
Recurrent disease	6	7.6
Miscellaneous	6	7.6
Death with functioning graft	12	15.2

5, 10, and 15 years post-Tx, respectively (Fig. 2). The 10-year death-censored graft survival increased from 66% in 1987–1996 to 83% in 1997–2007 ($P = 0.02$). The overall graft and death-censored graft half-lives were 17.8 years (lower CI limit 14.1) and 20.1 years (lower CI limit 16.0), respectively. Variables that were associated with an increased risk of graft loss (including deaths) were glomerular diseases as primary disease and young recipients at Tx (<3 years) (supplementary Table S2). Investigation for an era effect revealed a significant interaction between age at Tx and era. Specifically, the higher risk of graft loss associated with young age at Tx was only present among those transplanted in the 1987–1996 period.

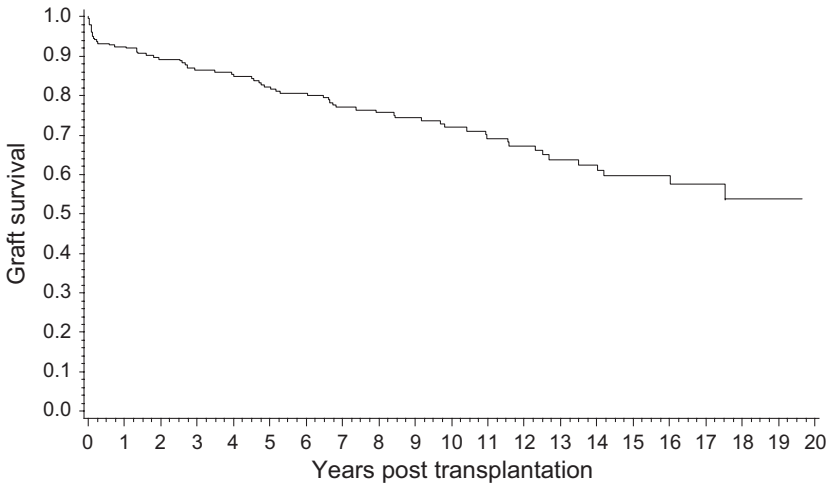
The same modeling procedure was performed in the subset of 213 Tx with a functioning graft beyond the first year post-Tx. In this subgroup, the variables associated with late graft loss in multivariable analysis were measured GFR at 1 year post-Tx, age at Tx $\geq$13 years and ARE within the first post-Tx year (supplementary Table S3). Poor HLA matching was a predictor of borderline significance. A significant interaction between ARE and era was seen, such that $\geq$1 ARE within 1 year post-Tx confers a higher risk for subsequent graft loss in the 1987–1996, but not in the 1997–2007 period. There was no era effect for any of the other variables in the final model. We found that gender, cold ischemia time, acute tubular necrosis, dialysis modality and duration, repeat Tx, donor age, and type did not significantly influence graft survival. LRD kidneys showed a greater 10-year survival compared with DD kidneys (80% vs. 68%), but the difference did not persist afterward (Fig. 3).

Malignancy

During follow-up, 16 of 219 patients developed a first malignancy at a median age of 15.7 years (range 3.1–24.9). The incidence rate of malignancy was 0.72 per 100 patient-years (CI 0.44, 1.17). The cancer type and outcome of patients have been previously described [16].

Growth

Among the 122 patients who reached adulthood, data on height were available in 118. Height SDS did not change signifi-



Follow-up	Baseline	5 years	10 years	15 years	20 years
N at risk	240	182	87	36	3
Survival	100	82 [CI 77, 87]	72 [CI 65, 78]	59 [CI 51, 68]	51 [CI 40, 62]

Figure 2 Death-censored graft survival after renal transplantation.

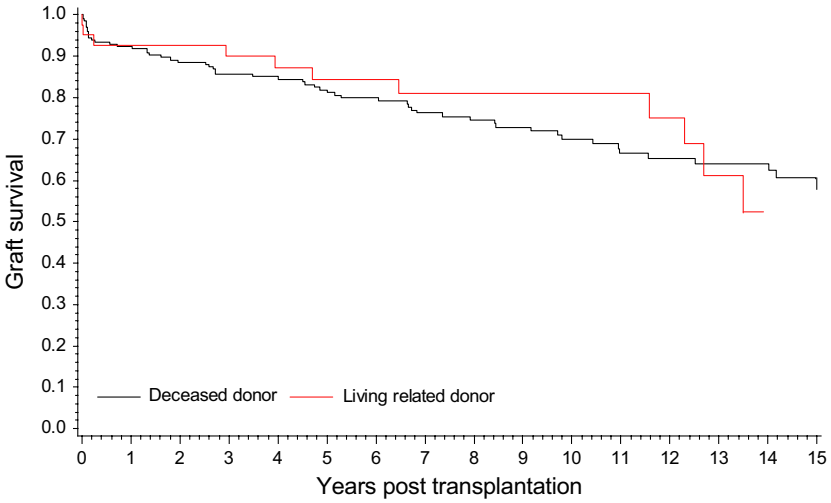


Figure 3 Graft survival according to donor type.

cantly between the age at Tx (−1.7 SDS ± 1.6) and the time of transfer to adult unit at a median age of 18.4 years (−1.6 SDS ± 1.3). At that age, 32% of patients have not reached a normal adult height, i.e. height SDS ≥ -2. However, 20% of patients had a growth velocity >1 cm/year at the time of transfer and were considered to have not reached their final height. Median height of boys was 166 cm (IQR 160–171) corresponding to a median height SDS of −1.5 (IQR−2.4 to −0.6). Median height of girls was 152 cm (IQR 147–156) corresponding to a median height SDS of −2.0 (IQR −2.8 to −1.1). In multivariable analysis, adult height SDS was positively associated with height SDS at Tx ($P < 0.01$), age at Tx ($P = 0.03$), and measured GFR at 1 year post-Tx ($P = 0.05$). Height SDS at transfer improved significantly ($P < 0.01$) over time from −2.0 SDS (IQR −3.2 to −1.1) in patients transplanted in the 1987–1990 period to −0.8 SDS (IQR −1.4 to 0.4) in those transplanted from 2001 onwards (Fig. 4). Improvement of adult height by Tx periods remained significant after adjustment on sex and age at Tx. Eleven children (9%) received growth hormone (rhGH) after Tx and showed increased height SDS from −2.5 at Tx to −1.8 at transfer.

Education and social outcome

Information about education and employment was available in 92 of 122 patients transferred to adult units. Among them, 16 (17.4%) belonged to neither in employment, nor in education or training (NEET) group and were considered as disadvantaged youth. This proportion was about 11.5% in French inhabitants aged 15–29 years in 2007 according to the Organisation for Economic Co-operation and Development statistics.

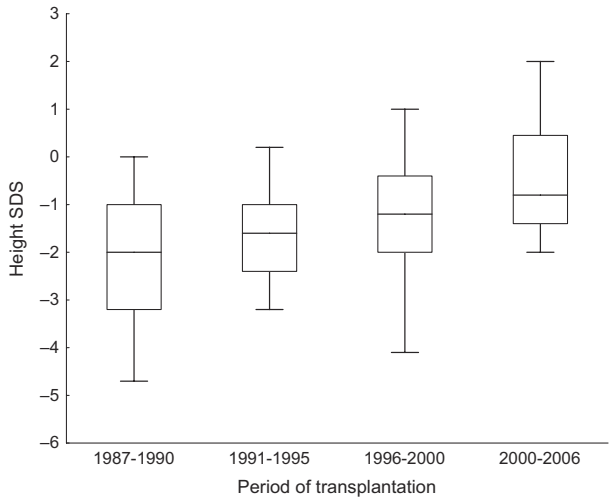


Figure 4 Adult height SDS according to the era of transplantation (n = 118). Boxplots with 5th percentile, 25th percentile, median, 75th percentile, and 95th percentile.

Discussion

This study presents the short- and long-term outcomes of a pediatric renal transplant cohort over a 20-year period. Although the retrospective analysis and the relatively small number of events are important limitations to this study, this is one of the largest single-center report on long-term outcomes in pediatric renal Tx. Along with the review of patients charts, the extraction of data from national registries allowed us providing updated and reliable information on the occurrence of death, graft loss, and cancer in patients followed in adult-care units.

The main findings of this study are as follows: (i) pediatric kidney recipients had a 15-year survival rate >90%; (ii) survival may be lower in the youngest recipients; (iii) graft survival improved over time yielding an expected death-censored graft half-life of 20 years; (iv) long-term graft survival is lower among adolescents than among younger recipients; (v) final height was reduced compared with the general population, but improved by Tx eras.

The mortality rate in children with ESRD may be 30 times as high as in age-related healthy population, although pediatric transplant recipients consistently have up to a fourfold survival benefit compared with dialysis patients [17,18]. Data from our study and those of other long-term follow-up reports [10,11,19–21] suggest that a patient survival of >85% at 10–20 years post-Tx should now be a reasonable expectation. Infections and malignancies were the major causes of death while cardiovascular disease was relatively uncommon compared with other centers [11,22]. Consistent with some reports [22], but in contrast with others [23], we found a worse survival in the youngest age group. Results from a large study from the USRDS recently confirmed that the youngest recipients have higher mortality rates and standardized mortality ratios than older children, particularly in the first year post-Tx [24]. However, given the small number of patients and small number of events [5 of 26 (19%) children <3 years of age at Tx died vs. 12 of 183 (7%) among older children], our finding should be interpreted with caution. We observed long-term graft survival of 67–72% and 55–59% at 10 and 15 years, respectively, resulting in high graft half-lives of 18–20 years. Other long-term studies reported lower rates of 45–66% at 10 years, 35–46% at 15 years, and 30–40% at 20 years, but all these studies included early eras with data from the 1970s [9–11,19,20]. Consistent with the aforementioned reports, a substantial increase in graft survival was seen during the last period of our study. Some reports showed that age, ARE, donor source, and primary disease are important predictors of graft survival [25,26]. In our study, the steady increase in late graft survival may be because of the era effects for age and ARE, such that young age and ARE within 1 year post-Tx were not associated with graft failure in the second Tx decade. We found as others that graft survival was poorer in adolescents without improvement over time suggesting that emphasis on medication adherence in this age group remains of major importance [26,27]. We found a 12% better graft survival of LRD over DD kidneys at 10 years, but this benefit was lost thereafter. Explanations may involve lack of statistical power as well as similar long-term consequences of noncompliance and calcineurin inhibitors toxicity in LRD and DD Tx [11].

Although not significant, poor HLA matching tended to predict graft survival. Data from the UK demonstrated a twofold increased risk of late graft loss associated with two HLA-DR mismatches in pediatric recipients [25]. In contrast, in the context of the current organ allocation policy in the United States, Gritsch *et al.* showed no effect of HLA-DR matching on 5-year graft survival in 1585 transplanted children [28]. However, children who receive HLA-DR mismatched kidneys might be exposed to more intensive immunosuppression to overcome the potentially increased risk of acute rejection, and therefore to a higher risk of malignancy as recently reported [29].

Pediatric transplant recipients have an increased risk of cancer with an estimated standardized rate ratio of 15–30 compared with the general population [30], the most common forms of malignancies being non-Hodgkin lymphomas and skin cancer at older age. However, data on the long-term risk of malignancy in children who underwent renal Tx are scarce. In our study, a total 7.3% of 219 patients developed malignancy over a median follow-up of 10 years. A German cohort study (mean follow-up 13 years) of 150 transplanted children found a rate of

malignancies of 2.6% [19]. Bartosh *et al.* reported 12% malignancies in 57 adults (mean age 31 years) transplanted during childhood [31]. In the Dutch national long-term follow-up cohort, 8.4% of 249 patients developed malignancies resulting in a 17% incidence 25 years after the start of RRT [32]. With the current use of more intense immunosuppressive regimens, which can compromise patient's immune surveillance mechanism for tumor cells and mediate infections from oncogenic viruses, malignancy after childhood Tx might become an even more prevalent problem in the near future [33].

Adults who were transplanted during childhood are often dissatisfied with their final height, and short stature has been associated with a lower marital status, a lower level of education, and a lower level of employment [34,35]. In our study, more than two-thirds of the patients were within the normal range, but remained far below the general population with a height of 152 and 166 cm, respectively, for girls and boys at the time of transfer. The use of rhGH after Tx has been suggested to improve the final height [36]. We cannot draw a conclusion about its effect in our study as only a small proportion received rhGH. Moreover, height SDS did not change significantly between the age at Tx and the age at transfer in our study. The observed improvement in final height achievement over time therefore rather reflects better pre-Tx management than catch-up growth post-Tx. In the future, steroid withdrawal or avoidance protocols may represent a good opportunity to optimize final height after Tx [37]. The information on social issues we were able to collect was unfortunately limited. As others, we found a higher proportion of disadvantaged youth in transplanted patients than in age-related healthy population despite a good employment rate [11,35].

In conclusion, continuous improvement is ongoing and excellent long-term outcomes can now be achieved in pediatric renal Tx. However, specific problems such as adolescent adherence, malignancies, growth, and social outcome affect quality of life and deserve priority research.

Authorship

JH and PC: designed the research and wrote the article. JH: performed statistical analyses. BR: analyzed data and contributed to the drafting of the article. AB-T, GM, JB, LB, OB, RB, DD, LD, DF, and XM: participated to data collection and provided intellectual content of critical importance. Each author listed on the manuscript read and approved the submission of this version and takes the full responsibility for the manuscript.

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Supporting Information

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

Table S1. Factors associated with mortality using Cox regression model ($n = 219$ patients).

Table S2. Factors associated with overall graft loss using Cox regression model ($n = 240$ Tx).

Table S3. Factors associated with graft loss beyond first year post-transplantation using Cox regression model ($n = 213$ Tx).

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