ORIGINAL ARTICLE

Outcomes of kidney transplantations in children weighing 15 kilograms or less: a retrospective cohort study

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SUMMARY

Kidney transplantation (KT) is often delayed in small children because of fear of postoperative complications. We report early- and long-term outcomes in children transplanted at ≤15 kg in the two largest Belgian pediatric transplant centers. Outcomes before (period 1) and since the introduction of basiliximab and mycophenolate-mofetil in 2000 (period 2) were compared. Seventy-two KTs were realized between 1978 and 2016: 38 in period 1 and 34 in period 2. Organs came from deceased donors in 48 (67%) cases. Surgical complications occurred in 25 KTs (35%) with no significant difference between the two periods. At least one acute rejection (AR) occurred in 24 (33%) KTs with significantly less patients experiencing AR during period 2: 53% and 12% in period 1 and, period 2 respectively ($P < 0.001$). Graft survival free of AR improved significantly in period 2 compared with period 1: 97% vs. 50% at 1 year; 87% vs. 50% at 10 years post-KT ($P = 0.003$). Graft survival tended to increase over time (period 1: 74% and 63% at 1 and 5 years; period 2: 94% and 86% at 1 and 5 years; $P = 0.07$), as well as patient survival. Kidney transplantation in children ≤15 kg remains a challenging procedure with 35% of surgical complications. However, outcomes improved and are nowadays excellent in terms of prevention of AR, patient and graft survival.

Transplant International 2018; 31: 720–728

Key words
acute rejections, graft survival, kidney transplantation, patient survival, pediatric, small children

Received: 16 October 2017; Revision requested: 12 November 2017; Accepted: 15 December 2017; Published online: 19 January 2018

Introduction

Infants and small children represent a small minority of all patients with end-stage renal disease (ESRD) needing renal replacement therapy (RRT). In a 2011 English survey, children younger than 24 months accounted for less than 2% of all pediatric patients with ESRD and for less than 0.3% of pediatric transplantations [1]. In the

doi:10.1111/tri.13108

North American Pediatric Renal Trial and Collaborative Studies (NAPRTCS) registry reporting the data on pediatric renal transplantation between 1987 and 2010, children younger than 12 months accounted for about 5% of the transplant recipients younger than 18 years of age [2].

Kidney transplantation (KT) represents the best treatment modality for children with ESRD and should be performed as early as possible, as outcomes are superior to dialysis in terms of growth, neurocognitive development, and quality of life [3].

In the '80s, the first experiences of KT in infants have been disappointing, due to the high number of vascular complications and acute rejections (ARs). Short- and long-term results have improved over time. However, most centers are still reluctant to transplant children weighing below 10 to 15 kg because transplantation of these very small patients remains uncommon and challenging with a high risk of surgical and nonsurgical complications [3,4]. The first objective of this retrospective cohort study was to review early postoperative outcomes after KT in small children in Belgium. In addition, we evaluated the evolution of KT over time in terms of incidence of AR as well as patient and graft survival at 1, 5, and 10 years, comparing two groups, before and since 2000. This date reflects the introduction of basiliximab as the standard induction treatment and the replacement of azathioprine (AZA) by mycophenolic acid (MPA).

Materials and methods

The study is a retrospective cohort study including all children weighing ≤15 kg transplanted between August 1, 1978, and March 31, 2016, in the two main Belgian pediatric renal transplantation centers: Hôpital Universitaire des Enfants Reine Fabiola (HUDERF) in Brussels, and University Hospitals Leuven. The present cohort therefore represents the large majority of renal transplantations realized in children weighing ≤15 kg in Belgium.

Data from these children were retrieved from the medical files at both centers. One patient transplanted in 1978 was excluded from the analysis due to the lack of clinical information. The analyzed data comprise patient demographics, KT information, early surgical complications, delayed graft function (DGF), AR episodes, and data on patient and graft survival.

Early surgical complications were defined as complications potentially requiring a surgical reintervention and occurring in the period between the transplant surgery and the discharge of the patient.

Delayed graft function was defined as the need for dialysis during the first post-transplant week.

Acute rejection was defined as an acute deterioration in allograft function associated with diagnostic histopathological features on kidney allograft biopsy, following local protocol before 1993 and the Banff classification thereafter [5]. Early acute rejection (EAR) referred to a rejection that developed during the first 3 months after transplantation. The 38 years of pediatric transplantation experience have been divided into two periods, before 2000 (period 1) and since 2000 (period 2). This date reflects the introduction of new immunosuppression regimens: basiliximab as the standard induction treatment and the replacement of azathioprine (AZA) with mycophenolic acid (MPA). The year 2000 also corresponded to the introduction of tacrolimus in pediatric transplantation in Belgium.

Numerical results have been presented as proportions for categorical variables, means with standard deviation for normally distributed continuous variable, or medians with interquartile range (IQR) for other continuous variables. Hypothesis testing to compare categories was carried out with the Student's *t*-test for normally distributed continuous variables and the Wilcoxon rank sum test for other continuous variables. Differences between categorical variables were compared using the chi-squared test or Fisher Exact test in case of small samples. The effect of confounders on the risk of acute rejection was investigated by pairwise adjustments using logistic regression modeling, as the number of events of interest was insufficient for a full multivariate model. For calculation of death-censored graft loss (DCGL), patients dying with a functioning graft were censored on the last day of survival. For calculation of patient survival, deaths occurring during the first three months after returning to dialysis were taken into account. Two patients died early after returning to dialysis and were therefore considered to have the event of interest for both death-censored graft loss and patient death. The Kaplan–Meier method was used to estimate graft survival, and the effect of covariates on graft loss was modeled using the Cox proportional hazard model. Because of an insufficient number of transplantations in the later period with follow-up of more than 10 years, survival analysis was restricted to 10 years of follow-up in the Cox model. The proportional hazard assumption was tested by visually inspecting the graphs of – log survival in function of log time for the different covariates, and by testing the null hypothesis of no change in Schoenfeld residuals over time.

For data analysis, we used Microsoft Excel 2010 and STATA 12 for Windows (StataCorp LP, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

The study protocol was reviewed and approved by our local Ethics Committee. To guarantee data confidentiality, data were anonymized, birthdates deleted after the age had been calculated, and the data file conserved on a password-protected laptop computer.

Results

Patient and donor characteristics

A total of 72 renal transplantations were performed on 68 children weighing ≤15 kg in the two main Belgian pediatric transplant centers between August 1, 1978, and March 31, 2016. Thirty-eight transplantations (53%) have been performed before 2000 and 34 (47%) since 2000.

The causes of end-stage kidney disease are presented in Table 1. The primary disease varied between the two studied periods with congenital anomalies of kidney and urinary tract (CAKUT) being the most common etiology in period 1 and congenital nephrotic syndrome (CNS) in period 2.

The characteristics of the patients and transplantations are shown in Table 2. The median age of recipients at first transplantation was 3.2 years (IQR, 2.3–3.9) and the mean body weight was 12.0 ± 1.9 kg. Compared with the children transplanted in period 2, the patients transplanted in period 1 were similar in terms of age but significantly smaller: mean weight of 11.2 kg vs. 12.8 kg ($P < 0.0005$); median height of −3.1 SD vs. −2.3 SD ($P = 0.03$) [6].

Forty-eight (67%) KTs were performed with an organ procured from deceased donors: 23 (61%) in period 1 and 25 (74%) in period 2 ($P = 0.24$). Although not statistically significant, the median age of donors increased from 6.5 (IQR, 3.0–21.5) years in period 1 to 18.0 (IQR, 6.0–23.0) years in period 2 in deceased donor transplantations. Cold ischemia decreased significantly from a median of 22 h (IQR, 15–25) to 15 h (IQR, 13–18) over time ($P = 0.02$).

Seven (10%) patients received a combined kidney–liver transplantation. Characteristics and outcomes are shown in Table S1.

Immunosuppression

Apart from the steroid treatment, which has been used in all 72 KTs, immunosuppression regimen has changed over time.

Table 1. Primary renal diseases in 68 children weighing ≤15 kg at transplantation. The causes of end-stage kidney disease are also shown for the two periods, before and since 2000.

Primary renal disease	Total patients ($n = 68$)	Before 2000 ($n = 34$)	Since 2000 ($n = 34$)
CAKUT total, *n* (%)	29 (43)	18 (53)	11 (32)
Obstructive uropathy	12	11	1
Hypo-/dysplasia with and without vesico-ureteric reflux	17	7	10
NS, *n* (%)	24 (35)	8 (24)	16 (47)
NPHS1	9	1	8
PLCE1	4	2	2
NPHS2	1	1	0
WT1-Denys-Drash Syndrome	2	0	2
ACTN4	1	0	1
LAMB2	1	1	0
No mutation found	6	3	3
Hyperoxaluria	4	3	1
ARPKD	3	1	2
Nephronophthisis	3	2	1
Hemolytic Uremic Syndrome	2	1	1
Bilateral Wilms tumor	1	0	1
Shock	1	0	1
Unknown	1	1	0

CAKUT, congenital anomalies of kidney and urinary tract; NS, nephrotic syndrome; ARPKD, autosomic recessive polycystic kidney disease.

Before 2000, 14 KTs (37%) were performed without induction therapy and 24 (63%) with antilymphocyte antibodies. Since 2000, 33 of 34 KTs were performed using an induction treatment: anti-ILR2 antibodies in 32 KTs and antilymphocyte antibodies in 1 KT.

Before 2000, nine KTs (24%) were performed without CNIs. Cyclosporine A (CsA) was administered in 29 KTs (76%), while tacrolimus (TAC) was not in use in the pediatric patients during this period. Since 2000, a CNI treatment was used in all transplantations: CsA in 20 KTs (59%) and tacrolimus (TAC) in 14 KTs (41%).

Before 2000, no antiproliferative medications were prescribed in three KTs (8%), azathioprine (AZA) was used in 34 transplantations (89%), and mycophenolic acid (MPA) in only 1 KT. Since 2000, an antiproliferative drug was used in all transplantations: MPA in 31 KTs (91%) and AZA in three KTs (9%).

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Table 2. Characteristics of the patients and transplantations.

	Total	Before 2000	Since 2000	*P*
Patients				
No. patients total	**68**	**34**	**34**	*p*=1
Boys, *n* (%)	44 (65)	25 (74)	19 (56)	0.07
Age at time of diagnosis, median (IQR), months	0.7 (0 to 6)	0 (0 to 5.25)	1 (0 to 11.75)	0.15
Age at 1st transplantation, median (IQR), years	3.2 (1.3 to 11.3)	3.0 (1.3 to 6.9)	3.4 (1.5 to 11.3)	0.33
Time in dialysis before 1st transplantation, median (IQR), months	13 (7 to 19)	12 (7 to 17)	14 (8 to 19)	0.21
Weight at 1st transplantation, mean (SD), kg	12 (±1.9)	11.2 (±1.9)	12.8 (±1.5)	<0.0005
Height at 1st transplantation, median (IQR), SD	−2.8 (−3.8 to −1.9)	−3.1 (−3.9 to −2.4)	−2.3 (−3.4 to −2.2)	0.03
Transplantations				
Transplantations, *n*	**72**	**38**	**34**	*p*=0.5
Deceased donors, *n* (%)	48 (67)	23 (61)	25 (74)	0.24
Living donors, *n* (%)	24 (33)	15 (39)	9 (26)	
Mother	10 (14)	8 (21)	2 (6)	
Father	14 (19)	7 (18)	7 (21)	
Age of donors (whole cohort) median (IQR), years	23 (7 to 31.2)	26 (4.0 to 31.2)	21.5 (10 to 33)	0.84
Age of deceased donors, median (IQR), years	15 (3 to 23)	6.5 (3.0 to 21.5)	18 (6.0 to 23.0)	0.28
HLA incompatibilities, median	3	3	3	0.87
Transplanted organs, *n*	65 kidney 7 kidney-liver	34 kidney 4 kidney-liver	31 kidney 3 kidney-liver	
Cold Ischemia time (whole population, median (IQR), hours	13 (3 to 20)	10 (2 to 24)	13 (8 to 17)	0.92
Cold Ischemia time (deceased donors), median (IQR), hours	16 (13 to 22)	22 (15 to 25)	15 (13 to 18)	0.02
DGF (whole cohort), *n* (%)	14 (19.4)	9 (23.7)	5 (14.7)	0.38
DGF (deceased donors) *n*/Tot (%)	9/47 (19.2)	7/23 (30.4)	2/25 (8)	0.068
Warm Ischemia, median (IQR), minutes	40 (36 to 48)	39 (35 to 45)	45 (36 to 51)	0.07

P, P value of null hypothesis of comparison before and since 2000; SD, standard deviation; IQR, interquartile range P25–P75.

Early surgical complications

Overall, early surgical complications were observed in 25 (35%) transplantations, with 19 (26%) requiring at least one reintervention. Of these 19 reinterventions, six were vascular, five urological, three explorative surgeries, two reinterventions were motivated by a donor–recipient size incompatibility, and three by other reasons. The details of the various surgical complications are shown in Fig. 1. Although not significant, a lower incidence of early surgical complications has been observed in the second group: 16 (42%) in period 1 and nine (26%) in period 2 ($P = 0.16$). Of all surgical complications, vascular complications (including vascular stenosis, renal vascular thrombosis, and hemorrhage) were the most frequent ($N = 12$ of 25, 48%). Vascular complications tended to occur more frequently during period 1 when compared to period 2: nine vascular complications over 38 KTs (24%) versus three vascular complications over 34 KTs (9%) ($P = 0.12$).

Of the 12 KTs which presented a vascular complication, three (25%) ended with a graft lost within the 3 months post-transplantation, and these three KTs had all been performed in period 1. Delayed graft function (DGF):

The number of grafts with DGF also tended to decrease over time, from 9 (24%) in period 1 to 5 (15%) in period 2 ($P = 0.38$). When restricting the analysis to deceased donor transplantations, this difference became nearly significant: period 1, $N = 7$ (30%) and period 2, $N = 2$ (8%) (Table 2; $P = 0.068$).

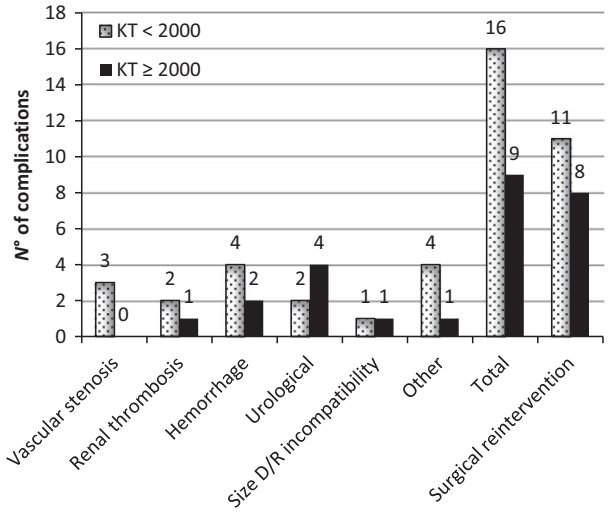

Figure 1 Early surgical complications after kidney transplantation.

Acute rejections

At least one episode of biopsy-proven AR was reported in a total of 24 transplantations (33%) during the entire follow-up period.

Before 2000, 20 KTs (53%) were complicated by an AR: 17 were EAR (85%), and three occurred more than 90 days after the intervention (15%). Since 2000, four KTs were complicated by an AR (12%) and no EAR was observed. During period 1, transplantation survival free of AR at 1-year post-KT was 50% (95% CI 33–65) and remained the same at 5 and 10 years. During period 2, transplantation survival free of AR increased to 97% (95%CI 79–100), 92% (95% CI 71–98), and 87% (95% CI 64–96) at 1, 5, and 10 years post-KT, respectively ($P = 0.0003$) (Fig. 2). No significant difference in AR incidence was found between living ($N = 10$, 42%) and deceased donors ($N = 14$, 29%).

Several patient and transplant characteristics differed over time (Tables 1 and 2) and might have therefore confounded the strong association between period and AR (OR 8.3; 95% CI 2.5 to 28.3; $P = 0.001$). CAKUT as primary kidney disease and male gender were associated significantly with an increased risk of AR (Table S2). Adjustment for different patient and transplant characteristics did not significantly alter the effect of period on AR (Table S3). None of the other variables remained significantly associated with the risk of AR after adjustment for period (Table S2).

Cancers

Overall, four patients developed a cancer: two post-transplantation lymphoproliferative disorders (PTLD) in period 1 and two PTLD in period 2. They occurred at 2.6 and 10.9 years post-transplantation in the patients transplanted before 2000, and at 6 months and 2 years post-transplantation in the patients transplanted in the most recent period. All the four patients were successfully treated with reduction of immunosuppression and chemotherapy.

Patient survival

During the entire follow-up period, eight deaths occurred (11%). The overall patient survival was of 92% (95% CI 83–97%) at 1 year and 91% (95% CI 80–96%) at 5 and 10 years post-KT. In period 1, six deaths occurred: five (one pneumocystis infection, one shock,

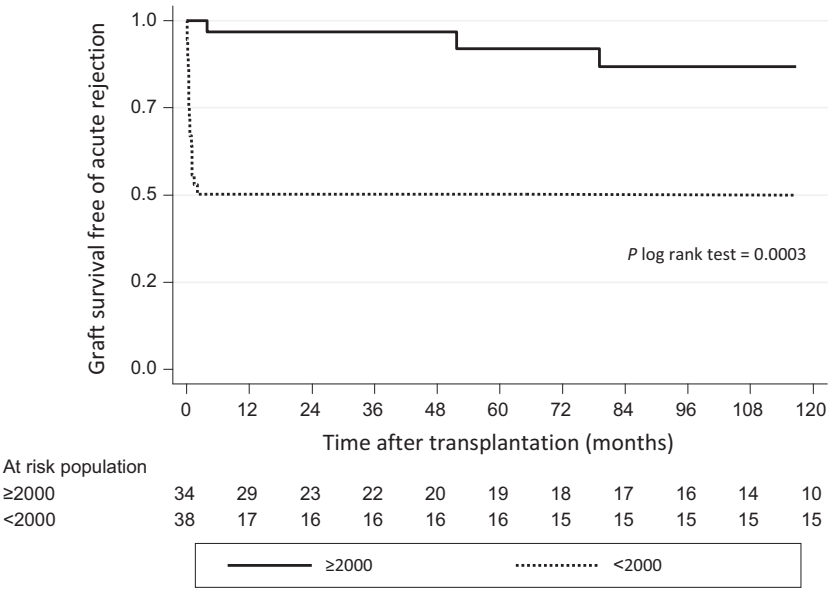

Figure 2 Graft survival free of acute rejection for the two transplant periods (before and since 2000).

three graft losses with impossibility to restart dialysis therapy) in the early post-transplantation period and one due to a septicemia more than 10 years after transplantation. In period 2, two deaths have been observed, one early due to a septic shock and the other one at more than 10 years post-KT due to dehydration while on holidays in Africa. Kaplan–Meier estimates of patient survival were 87% (95% CI 70–94) at 1 year and 84% (95% CI 68–92) at 5 and 10 years post-KT for period 1 and 97% (95% CI 80–100) at 1, 5, and 10 years post-KT for period 2 ($P = 0.2$) (Fig. 3).

Graft survival

Kaplan–Meier estimates of overall graft survival, taking patient death and return to dialysis into account for graft failure, were 74% (95% CI 57–85) at 1 year, 66% (95% CI 48–78) at 5 years and 58% (95% CI 40–72) at 10 years in patients transplanted before 2000 as compared to 94% (95% CI 78–98) at 1 year and 86% (95% CI 66–95) at 5 and 10 years post-transplantation for patients transplanted since 2000 ($P = 0.07$, Fig. 4a).

During the entire follow-up period, 27 transplant recipients returned to dialysis therapy (38%). The death-censored Kaplan–Meier graft survival estimates were 88% (95% CI 78–94) at 1 year, 81% (95% CI 69–89) at 5 years, and 76% (95% CI 63–85) at 10 years post-KT.

Twenty-two grafts (58%) were lost in patients transplanted before 2000, and five (15%) in those transplanted since 2000. During the two consecutive periods, Kaplan–Meier estimates of death-censored graft survival were 83% (95% CI 67–92) at 1 year, 77% (95% CI 59–88) at 5 years, and 68% (95% CI 49–81) at 10 years in patients transplanted before 2000 as compared to 94% (95% CI 78–98) at 1 year and 86% (95% CI 66–95) at 5 years and 10 years post-transplantation for patients transplanted since 2000 ($P = 0.22$. Fig. 4b). Transplantation before 2000 was associated with a hazard ratio (HR) of 2.46 (95% CI 0.78 to 7.73) that did not attain statistical significance. AR (HR 6.0; 95% CI 1.91 to 18.89; $P = 0.002$) and DGF (HR 4.29; 95% CI 1.52 to 12.14; $P = 0.006$) were the only risk factors associated with a significant increase in DCGL in the univariate Cox models. Both AR and DGF were more frequent before 2000. Adjustment for these two variables in the Cox model reduced the HR associated with transplantation before 2000 to 1.10 (95% CI 0.31 to 3.84), suggesting that most of the improved death-censored graft survival after 2000 was due to a lower incidence of DGF and better prevention of AR (Table S3).

Discussion

The first attempts of KT in infants (0–24-month-old) were performed in the 1960s by J S Najarian and collaborators in Minneapolis [7,8]. The outcomes were at first disappointing, which led to an overall questioning of the rational to provide renal replacement therapy (RRT) in very small children with ESRD. In the 1980s, improvements in dialysis, surgical transplant techniques, and immunosuppressive medication dramatically improved the overall results of RRT in children. This also led to a gradual acceptance of these therapies for infants with ESRD [3,4,7,9]. Although considerable advances have been achieved over time in terms of

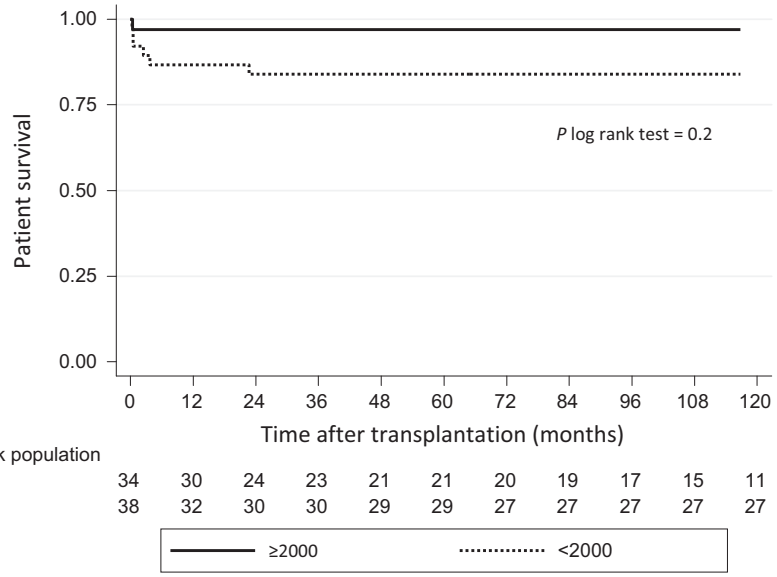

Figure 3 Patient survival for the two transplant periods (before and since 2000).

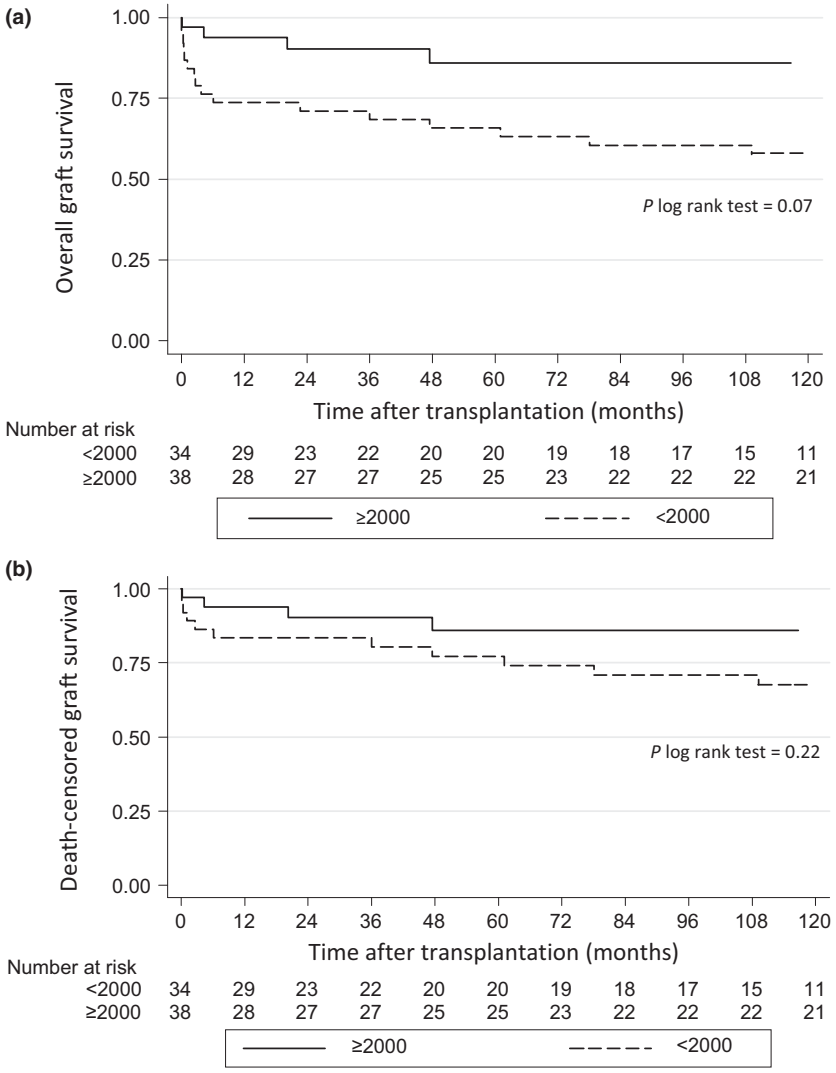

Figure 4 (a) Overall graft survival for the two transplant periods (before and since 2000). (b) Death-censored graft survival for the two transplant periods (before and since 2000).

decrease in AR, and improvements in patient and graft survival, kidney transplantation in these small children remains quite a rare and challenging procedure. Nowadays, the potential early surgical and nonsurgical complications leading to graft loss are still a source of concern. Particularly, frightening are the dramatic complications such as vascular thrombosis, massive hemorrhage, and vascular stenosis.

Our cohort includes all transplantations realized in children ≤15 kg in the two main pediatric transplantation centers in Belgium, starting with the first surgery performed in 1978. The overall risk of surgical complications in our patients is important: They occurred in about one-third of all transplantations, and approximately one every four KT needed a reintervention. However, we observed a progressive reduction of these complications over time, in particular for the vascular problems. In the transplantations realized before 2000, vascular stenosis, thrombosis, or hemorrhages occurred in nearly 25% of KT, while they fell to less than 10% of KT for those performed since 2000.

Similar substantial improvements over time have been observed for the occurrence of delayed graft function. It is well known that DGF is the result of different causes, such as a long cold ischemia time, extreme donor's age, and immunological injury. It is associated with a higher risk of AR and is a detrimental factor for graft survival at short and longer term [10,11]. In one single-center study of 518 patients, multivariate analysis found that DGF was the major accountable factor for kidney survival at one year [11,12].

In our cohort, DGF occurred in about 30% of the transplantations performed before 2000 and dropped to less than 10% in the KT performed since 2000. Decreased cold ischemia time, exclusion of very young donors, and better immunological management are probably the main underlying reasons for this current low incidence of DGF.

In our population, the rate of AR decreased impressively over time, and in particular, early AR has become an exceptional event. Before 2000, AR occurred in more than half of the transplantations and most of these rejections were observed within the first 3 months. Since 2000, AR occurred in about one over 10 grafts performed, and no more early AR were seen. For the KT realized in this most recent period, the graft survival free of AR achieved rates of 97% and 87% at 1 and 10 years, respectively.

In terms of patient survival, our results in children transplanted (mostly from deceased donors) at a weight ≤15 kg show an increase in recipient survival at 10 years after transplantation from 84% for the KT performed before 2000 to 97% since 2000.

Similarly, in this time frame marked improvements have been observed in terms of graft survival, which increased from 74% to 94% at 1-year post-KT and from 57% to 86% at 10 years post-KT. These observations have to be interpreted with prudence in the context of the relatively small sample size of our study and the large confidence intervals of the survival estimates. In addition, only a small proportion of transplantations in the more recent period have a follow-up time of more than 10 years. The remarkable improvements in post-transplant outcomes in the more recent period have therefore to be confirmed by longer term follow-up.

Comparable improvements in outcomes over time were also observed in very small recipients of kidney transplants in the American and Scandinavian registries [4,13,14]. This contrast with a recent study of the University of Minnesota that has compared the outcomes of 136 infants transplanted in the three decades between 1984 and 2014 [15]. Although some improvements over time have been observed for the ten-year death-censored graft survival, the study could not show any significant difference between eras in patient survival and on the incidence of AR during the year after transplantation. While in the Minnesota study [15], the incidence of AR during the first post-KT year remained stable at about 30% during the entire period, in our cohort, we observed from period 1 to period 2 an approximately 80% reduction in the incidence of AR. The most probable reason for these differences is the replacement of the former immunosuppressive regimen consisting of induction with polyclonal antilymphocyte antibodies, cyclosporine, and azathioprine with the standard regimen of anti-ILR2 monoclonal antibodies, tacrolimus, and mycophenolic acid in our cohort whereas immunosuppression has remained unchanged in the US cohort [15].

Our data suggest that better prevention of DGF by shorting cold ischemia time and improved recipient management as well as optimal prevention of AR were responsible for the nearly twofold reduction of death-censored graft loss in the more recent period, although the present study was not powered to ascertain this in statistical terms.

Our cohort confirms that the more recent immunosuppressive drugs can be used in small recipients, and our data concur with others that in very small recipients, long-term patient and graft survivals are at present comparable, if not better, than in adult recipients [15,16].

Several other factors are probably responsible for all these remarkable improvements achieved in the last decades and for the current excellent outcome of kidney transplantation in very small children.

Children younger than 5 years are rarely accepted as donors, therefore reducing the risk of vascular complications during surgery. In our study, 14 patients received a graft from a donor younger than 5 years. Although not statistically significant because of the small sample size, in these 14 transplantations, we observed a percentage of DGF and graft loss in the first post-KT year more than double when compared to the transplantations performed with graft from older donors (data not shown).

Cold ischemia time has dropped, hence decreasing the incidence of DGF and AR, and improving at the same time the graft survival. The better fluid management during surgery has contributed to optimizing intra-vascular volume status, contributing to a lower risk of vascular thrombosis [17].

If AR becomes a rare complication, nowadays pediatric nephrologists are facing new challenges at short and longer terms.

These young recipients are often not immunized against immunomodulating viruses as EBV and CMV, and therefore are at particular risk of developing infections and/or cancers under the current strong immunosuppression [18]. Moreover, patients who received KT at a very young age need a follow-up and treatments for decades. The graft survival at longer term is often compromised by the irregular medical adherence, in particular at critical times as adolescence and/or transition to the adult medical care.

In conclusion, kidney transplantation in children ≤15 kg remains a challenging procedure with 35% of early surgical complications. However, outcomes are improved and are nowadays excellent in terms of prevention of AR as well as patient and graft survival.

Authorship

BC: was responsible for the design of the study, the recruitment of the data, the data analysis, and the draft of the manuscript. JH: was responsible for the recruitment of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. KL: participated in the recruitment of the data, the writing of the manuscript, and approved the final manuscript as submitted. BA: participated in the recruitment of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. EH, PL, TS, NK and DA: reviewed and revised the manuscript, and approved the final manuscript as submitted. KMW: participated in the design of the study, the data analysis, and the draft of the manuscript. He approved the final manuscript as summited. KI: was responsible for the design of the study and the writing of the manuscript.

Funding

No funding has been received for this work.

Conflict of interest

The authors declare no conflict of interests.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Characteristics and outcomes of the seven patients with combined kidney-liver transplantation.

Table S2. Effect of period on the odds of acute rejection after adjustment for potential confounders.

Table S3. Cox proportional hazard model of effect of period on death-censored graft loss after adjustment for acute rejection and delayed graft function [1,2].

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