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Chapter 7

The effect of timing of the first kidney transplantation on survival in children initiating renal replacement therapy

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Summary

Background. Controversy exists concerning the timing of the first kidney transplantation for children who need to start renal replacement therapy (RRT). Our aim was to estimate the effect of timing of the first transplantation on patient survival in children, for the first time also taking into account the mortality on dialysis before transplantation.

Methods. We included 2091 patients who started RRT between the age of 3 and 18 years in the period 1988-2007, from thirteen European renal registries. A multistate model was used to simulate patient survival assuming: a) pre-emptive transplantation; b) transplantation after one or two years on dialysis; and c) remaining on dialysis.

Results. Over the 20-year period the highest eight-year survival probabilities were achieved in children transplanted pre-emptively (living donor (LD): 95.9% (95% CI: 93.1-98.8), deceased donor (DD): 95.3% (95% CI: 90.9-99.9)) rather than after two years of dialysis (LD: 94.2% (95% CI: 91.6-96.8), DD: 93.4% (95% CI: 91.0-95.9)), although these differences were not statistically significant.

Conclusions. Even after taking mortality on dialysis into account, the potentially negative effect of postponing transplantation for one or two years was relatively small and not statistically significant. Therefore, if pre-emptive transplantation is not possible, starting RRT with a short period of dialysis and receiving a transplant thereafter seems an acceptable alternative from the perspective of patient survival.

Introduction

Kidney transplantation is generally considered the optimal form of renal replacement therapy (RRT) for children with end-stage renal disease. Compared to haemodialysis and peritoneal dialysis, kidney transplantation is associated with better patient survival [1-5], lower cardiovascular risk, better cognitive development, less growth impairment and better quality of life [6-8]. Children have a relatively high chance of a transplant since often a parent is willing to donate a kidney and in most countries children get priority on the waiting list for deceased donor (DD) kidneys. However, there is still some controversy concerning the timing of kidney transplantation relative to the initiation of dialysis, and although pre-emptive kidney transplantation (PKT), i.e. transplantation at the start of RRT, is promoted within the current policy [9,10], in practice this only happens in about 10 to 20% of the children starting RRT [3,4,11].

Several publications have demonstrated no influence on survival of a period of dialysis before kidney transplantation [12,13], while others have reported better patient survival after PKT [14]. The potential advantage of avoiding a period of dialysis would lie in the prevention of dialysis related cardiovascular disease, which is only partially reversible after kidney transplantation and the major cause of long-term cardiovascular morbidity and mortality [15,16]. However, previous survival comparisons included children only *after* they had actually received a kidney transplant and, therefore, only examined the survival from the time of transplantation. Hence, previous studies failed to take into account the deaths of patients who were on dialysis while they were waiting for a kidney transplant, thereby underestimating the difference between pre-emptive and post-dialysis kidney transplantation and biasing the results in favour of transplantation after a period of dialysis. Taking this 'early mortality on dialysis' into account in the survival analysis is important to help define the optimal timing of transplantation in relation to the initiation of RRT. The results of such an analysis as presented in this study will provide a more 'fair' comparison of survival between patients who received a pre-emptive transplant and those who started on dialysis and received a transplant later and will thereby further inform medical decision-making at the start of RRT.

By using a multistate model, we aimed to estimate the effect of timing of the first kidney transplant on patient survival in children, taking into account the mortality on dialysis before transplantation.

Materials and methods

Data collection

The European Renal Association - European Dialysis and Transplant Association (ERA-

EDTA) Registry currently collects individual patient data from European national and regional renal registries. Annually these registries send a data set to the ERA-EDTA Registry, including the following variables: a (meaningless) national registry patient identifier, date of birth, gender, primary renal disease, history of RRT with dates and changes of modality, treatment centre, date and cause of death, and information concerning transfer from or to other renal registries. The details of the methods used for data collection and data processing have been reported previously [17]. Data from the renal registries of Andalusia (Spain), Austria, Basque country (Spain), Catalonia (Spain), Denmark, Finland, Greece, Iceland, Norway, Scotland (UK), Sweden, the Netherlands and Valencian region (Spain) were included in this study because of the completeness and the availability of their paediatric data over a prolonged period.

Incident patients who started RRT during childhood (i.e. before reaching the age of 18 years) between 1 January 1988 and 31 December 2007 were included in the study. Patients who started RRT before the age of three years (N=476) and those who started RRT for end-stage renal disease due to haemolytic uraemic syndrome (N=55) or due to kidney tumours (N=15) were excluded from the study, as kidney transplantation in these patients was less likely (see questionnaire data in Results section). Furthermore, patients who received a kidney transplant from an unknown donor source (N=324) were excluded. Use of the registry data provided the possibility to follow patients for at least eight years, also after their eighteenth birthday. Primary renal diseases were defined according to the ERA-EDTA coding systems and were subsequently classified into categories [18]. Due to the great variety in the primary renal disease category 'Other' it was not possible to distinguish groups within this category.

To quantify the potential selection bias due to possible differences between children who started RRT with dialysis and those who received a pre-emptive transplant (i.e. confounding by indication) a questionnaire was developed to estimate how frequently kidney transplantation was denied or delayed and what the characteristics of these children were. This questionnaire was sent out to one paediatric nephrologist in each country that participated in this study.

Data analysis

We used a multistate model (Figure 1) to estimate the effect of timing of kidney transplantation on the patient survival of children starting RRT. A multistate model is a commonly used method to describe a process in which an individual moves through a series of non-overlapping "states" over continuous time [19-21]. Individuals can switch to another state at any moment in time, which is called a transition, or an event. Transition rates and the effect of covariables on these rates were modelled with Cox regression.

After eight years of follow-up less than 5% of the children who started RRT on dialysis were still on dialysis. For this reason, we chose to cut-off the patient follow-up at eight years.

Figure 1 shows that at any time point during this eight-year observation period, the children were in one of the following three states: (1) alive on dialysis (without previous transplant); (2) alive after first kidney transplant; or (3) deceased. Between the three states there were three possible transitions: (a) from 'alive on dialysis' to 'deceased', when a patient died while on dialysis; (b) from 'alive on dialysis' to 'alive after first kidney transplant'; and (c) from 'alive after first kidney transplant' to 'deceased'. As this research investigated the results of medical decision making *at the start of RRT* when a nephrologist will not know yet whether and when a child will lose its graft, it used an intention-to-treat approach. This means that patients who received a transplant and stayed alive during follow-up remained in the 'alive after first kidney transplant' state while taking into account their average risk of graft loss and of returning to dialysis and the influence of that on patient survival after transplantation.

The patient survival on dialysis, $S_D(t)$, was based on data from all children who started RRT with dialysis, including those who moved according to transition a (death as event of interest) or transition b (transplantation as censored observation) (see Figure 1). The patient survival after kidney transplantation, $S_{Tx}(t)$, was based on data from all children who had received a kidney transplant, including those who moved according to transition c (death as event of interest). To estimate $S_D(t)$ and $S_{Tx}(t)$ Kaplan-Meier method and Cox regression models were used. Starting points, events and censoring are described in Table 1. As the intention-to-treat principle was applied, graft failure and consequently going back to dialysis was not considered a censored observation for patient survival after first transplantation.

Data gained from the analyses with $S_D(t)$ and $S_{Tx}(t)$ were used to calculate the simulated survival probabilities (see Biostatistical technical notes) assuming the following hypothetical treatment scenarios:

- i) children remaining on dialysis for the entire period of RRT;
- ii) children receiving a kidney transplant at initiation of RRT (PKT); and
- iii) children receiving a kidney transplant after one or two years on dialysis.

The choice for one and two years was based on the distribution of the dialysis duration before transplantation in this study cohort: living donor (LD) kidney recipients received their

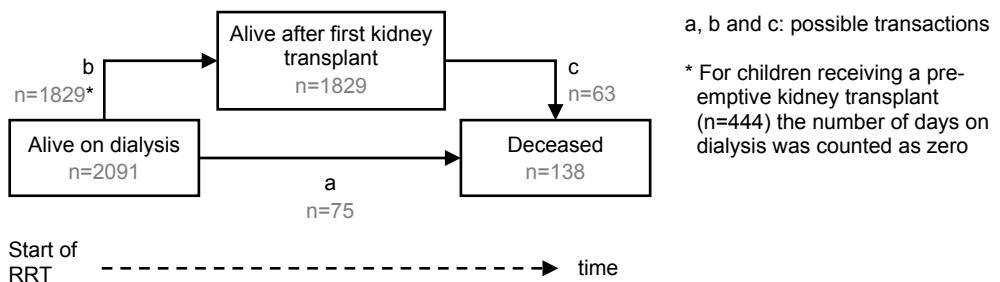


Figure 1. Graphical overview of the multistate model.

Table 1. Overview of events and censoring as defined for the survival analysis.

Survival type	Starting point	Event	Censoring
Patient survival on dialysis, $S_D(t)$	Start of dialysis	Death	Kidney transplantation End of follow-up (31/12/2007) Eight years after start dialysis Loss to follow-up Recovery of renal function
Patient survival after kidney transplantation, $S_{Tx}(t)$	Time of transplantation	Death	End of follow-up (31/12/2007) Eight years after transplantation Loss to follow-up Recovery of renal function

first transplant after an average of 0.2 year on dialysis and DD kidney recipients after an average of 1.0 year on dialysis. Moreover, after two years less than 22% of the patients who started RRT with dialysis were still on dialysis. The techniques used to combine the survival on dialysis and after transplantation allowed the calculation of 95% confidence intervals (CI) for this 'combined' survival, but not of hazard ratios (HR) and p-values to compare this combined survival. Nevertheless, non-overlapping 95% CIs after two, five and eight years of follow-up were considered to indicate a statistically significant difference between survival curves.

The simulated survival curves were adjusted for fixed values of the covariates age, gender, time period, and primary renal disease distribution according to the mean values and distribution of these covariates within the study population. The number needed to treat (NNT) to save one patient's life at eight years of follow-up was calculated by taking the inverse of the difference between two eight-year survival probabilities (for example between the simulated eight-year survival after pre-emptive transplantation and the simulated eight-year survival in the case of transplantation after one year on dialysis) [22].

As a sensitivity analysis, all simulations were repeated in a subcohort of patients excluding those with the following recurrent diseases as primary renal disease: focal segmental glomerulosclerosis, IgA nephropathy, membranoproliferative glomerulonephritis (Types I and II), Alport's Syndrome, primary oxalosis, lupus erythematosus and Henoch-Schoenlein purpura, as it was believed that having a potentially recurrent disease may influence the likelihood of transplantation [23].

The data analyses were performed using the statistical packages SPSS 16.0 [24] and R 2.9.0 [25]

Biostatistical technical notes

The Cox regression analysis for $S_D(t)$ and $S_{Tx}(t)$ provided the baseline hazard functions for survival on dialysis ($h_{0_D}(t)$), after pre-emptive kidney transplantation $h_{0_preTx}(t)$ and after

kidney transplantation after a period on dialysis ($h_{0_D_Tx}(t)$). In addition, Cox regression analyses provided the effect estimates (β) for the effect of covariables on survival on dialysis and after transplantation. Covariables included age at the onset of RRT (age at kidney transplantation in case of $S_{Tx}(t)$), gender, primary renal disease and year of onset of RRT (year of transplantation in case of $S_{Tx}(t)$). Based on the assumption that donor source and pre-emptive transplantation do not act independently, the effect of the combination of these variables on $S_{Tx}(t)$ was estimated. These baseline hazard functions and the effect estimates gained from $S_D(t)$ and $S_{Tx}(t)$ were used to simulate survival curves for fixed values of covariates.

The following formulae were applied for the simulated survival, $\zeta(t)$, according to the different treatment scenarios (t is the time from start of RRT and s is the time of the first kidney transplant):

- i) children remaining on dialysis for the entire period of RRT: here $\zeta(t) = S_D(t)$;
- ii) children receiving a kidney transplant at start of RRT: here the number of days on dialysis was counted as zero, i.e. $s=0$, and therefore $\zeta(t) = S_{Tx}(t)$;
- iii) children receiving a kidney transplant after one ($s=1$) or two years ($s=2$) on dialysis. Before the first transplant (i.e. as long as $t \leq s$) $\zeta(t) = S_D(t)$, and after transplantation (i.e. if $t > s$) $\zeta(t) = S_D(s) * S_{Tx}(t-s)$.

For example, if children were transplanted after one year on dialysis, i.e. $s=1$, then:

- $\zeta(t) = S_D(t)$ if $t < 1$,
- $\zeta(1) = S_D(1) * S_{Tx}(1-1) = S_D(1) * S_{Tx}(0) = S_D(1) * 1 = S_D(1)$, and
- $\zeta(t) = S_D(1) * S_{Tx}(t-1)$ if $t > 1$.

To be able to construct the survival for the latter treatment scenario we used methods that allow accounting for the increased (post-surgery) mortality right after transplantation.

Results

A total of 2091 children who started RRT between 1988 and 2007 were included in this study. An overview of the baseline characteristics at the onset of RRT and at the time of the first kidney transplant is shown in Table 2. Although only patients who started RRT before the age of 18 were included, in some patients transplantation was performed after the age of 18 years.

Single transition analysis

Of the 2091 children included in this study, 262 (12.5%) remained on dialysis for the entire period on RRT, 444 (21.2%) received a pre-emptive kidney transplant, and 1385 (66.2%) received a kidney transplant after a period on dialysis. Seventy-five children died without having received a kidney transplant (transition a in Figure 1). Table 3 shows that the patient

Table 2. Baseline patient characteristics.

Patient characteristics	At start of RRT				At time of first Tx	
	All patients N = 2091	Patients remaining on dialysis N = 262	Patients transplanted during follow-up		Transplanted patients	
			DD N = 1073	LD N = 756	DD N = 1073	LD N = 756
Age at start RRT (left 4 columns) / at Tx (right 2 columns) (%)						
3 - 6	12.8	11.1	13.7	12.2	8.9	11.0
7 - 10	20.1	11.1	21.2	21.7	18.3	19.8
11 - 14	29.6	25.2	32.9	26.3	28.6	25.7
15 - 17	37.5	52.7	32.2	39.8	26.8	33.1
18 - 27					17.4	10.5
Female gender (%)	42.9	41.6	43.8	42.1	43.8	42.1
Primary renal disease (%)						
Glomerulonephritis	13.6	8.4	13.9	14.9	13.9	14.9
Pyelonephritis	20.6	20.6	22.2	18.3	22.2	18.3
Cystic Kidneys	10.5	6.1	10.3	12.4	10.3	12.4
Hypoplasia / Dysplasia	15.2	10.7	14.8	17.2	14.8	17.2
Hereditary nephropathy	8.7	8.0	9.5	7.7	9.5	7.7
Other	31.5	46.2	29.4	29.5	29.4	29.5
Year in which RRT was started (left 4 columns) or Tx was performed (right 2 columns) (median (25 th -75 th percentile))	1998 (‘93 - ‘03)	2002 (‘94 - ‘06)	1996 (‘92 - ‘01)	1999 (‘94 - ‘03)	1998 (‘93 - ‘03)	2000 (‘95 - ‘04)
Years on dialysis till end of follow-up period (median (25 th - 75 th percentile))		2.2 (0.7 - 6.7)				
Pre-emptive Tx (N (%))			123 (11.5)	321 (42.5)		
Years on dialysis till first Tx (median (25 th -75 th percentile))					1.0 (0.4 - 1.9)	0.2 (0.0 - 0.7)
Years living with functioning transplant till end of follow-up period (median (25 th -75 th percentile))					7.5 (4.0 - 9.0)	7.4 (3.6 - 9.7)

Tx = transplantation; DD = deceased donor; LD = living donor

survival on dialysis without kidney transplantation, $S_D(t)$, improved with age at the onset of RRT (HR (95% CI): 2.00 (1.02-3.89) for children between three and six years of age compared to those aged 15 to 17 years). Survival on dialysis was also associated with primary renal disease category.

In total there were 1829 patients who received a first kidney transplant (transition b in Figure 1) during the study period (LD grafts 41.3% and DD grafts 58.7%), of whom 63 patients (14 after pre-emptive transplantation and 49 after transplantation after a period on

Table 3. Adjusted hazard ratios for the risk of death in children on dialysis, $S_D(t)$, and after kidney transplantation, $S_{Tx}(t)$.

Patient characteristics	On dialysis HR (95% CI)	After transplantation HR (95% CI)
Age at start RRT (left column) or age at transplantation (right column) (in years) ^a		
3 – 6	2.00 (1.02-3.89)	1.95 (0.93-4.11)
7 – 10	1.13 (0.57-2.24)	0.91 (0.43-1.95)
11 – 14	0.59 (0.30-1.15)	1.19 (0.63-2.28)
15 – 17	1	1
18 – 27	NA	1.08 (0.48-2.45)
Female gender	1.07 (0.67-1.70)	1.10 (0.68-1.78)
Primary renal disease ^a		
Glomerulonephritis	1	1
Pyelonephritis	1.11 (0.44-2.75)	0.48 (0.19-1.20)
Cystic Kidneys	0.72 (0.15-3.51)	0.65 (0.24-1.80)
Hypoplasia / Dysplasia	1.28 (0.43-3.86)	1.10 (0.48-2.52)
Hereditary nephropathy	1.26 (0.43-3.86)	1.58 (0.67-3.70)
Other PRD	3.02 (1.35-6.76)	0.98 (0.47-2.06)
Year in which RRT was started (left column) or transplantation was performed (right column)	0.98 (0.93-1.02)	0.96 (0.91-1.01)
Donor source and pre-emptive transplantation		
Deceased		0.97 (0.38-2.50)
Pre-emptive		1
Post-dialysis		
Living		0.67 (0.32-1.42)
Pre-emptive		
Post-dialysis		0.90 (0.50-1.61)

^a Variable associated with survival on dialysis ($p < 0.05$)

Analyses were adjusted for the other covariates in this table

dialysis) died within eight years after RRT initiation (transition c in Figure 1). Table 3 shows that for patient survival after transplantation, $S_{Tx}(t)$, none of the predictors were found to be statistically significantly associated with the risk of death.

Simulated RRT patient survival stratified by kidney donor source

By implementing the information (baseline hazards and effect estimates) gained from the survival on dialysis ($S_D(t)$) and after kidney transplantation ($S_{Tx}(t)$) into a multistate model, the effect of timing of transplantation on RRT patient survival was estimated. Figure 2 shows the simulated survival curves based on this cohort for four different groups: children who received a pre-emptive kidney transplant, who were transplanted after one or two years on dialysis or who stayed on dialysis for the entire period on RRT, stratified by the kidney donor source. After eight years on RRT the survival benefit for children transplanted pre-emptively compared to those who received a transplant after two years on dialysis was 1.9% (95% CI:

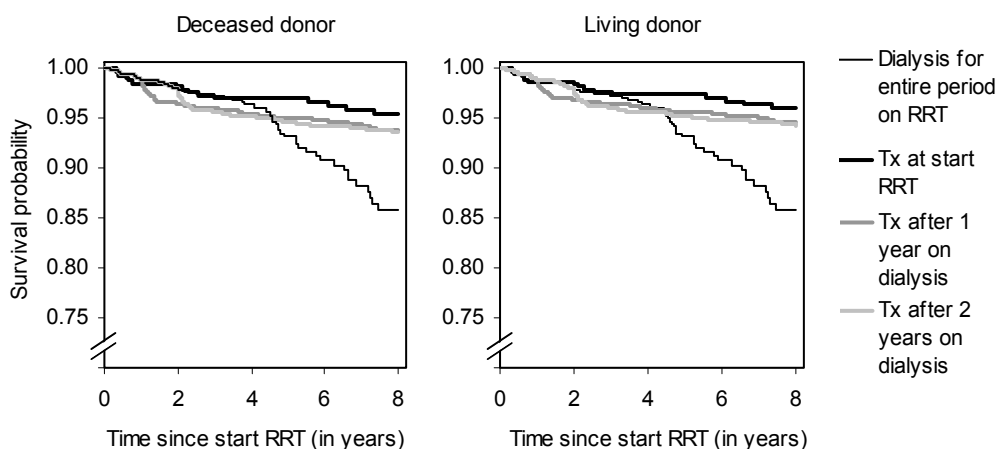
-3.2 to 7.0) for DD transplants and 1.7% (95% CI: -2.1 to 5.6) for LD transplants. So, the results suggested a minor survival benefit for children who were transplanted at the start of RRT, but the survival difference was not statistically significant. If we were to assume that this was a real difference, the number needed to treat (NNT) to save one life in eight years of follow-up with PKT instead of transplantation after one year on dialysis would be 61 (95% CI: 15 - 108) for DD transplants and 73 (95% CI: 18 - 127) for LD transplants. When comparing pre-emptive transplantation with transplantation after two years of dialysis, the NNT would be 53 (95% CI: 14 - 91) and 58 (95% CI: 17 - 98) for DD and LD kidney recipients respectively. Finally, when comparing transplantation after one year with transplantation after two years on dialysis the NNT would be 423 (95% CI: 27 - 819) and 275 (95% CI: 25 - 526) for DD and LD kidney recipients respectively. Furthermore, these graphs show that some of the curves cross due to the increased (post-surgery) mortality in the first months after transplantation. Consequently, after two years on dialysis the survival was 97.7%, whereas in patients who received a transplant after one year on dialysis the survival after two years was 96.4% in DD kidney recipients and 96.8% in LD kidney recipients.

Simulated RRT patient survival stratified by cohort of RRT initiation

Figure 3 shows the effect of timing of kidney transplantation on the simulated RRT patient survival in different decades, i.e. for children who initiated RRT in 1988 or in 1998, with averaged values of age, gender and primary renal disease. The differences in eight-year survival probabilities were not significant. Nevertheless, both graphs suggest that patients transplanted pre-emptively had the highest survival probabilities. Moreover, these graphs show that over calendar time survival differences between the scenarios decreased. This reduced difference in the most recent time period was due to an improvement of survival on dialysis affecting the survival times of children who received a transplant after an initial period on dialysis. As a result the potential disadvantage of a short-term period on dialysis before transplantation has decreased. In 1988, the eight year NNT with pre-emptive transplantation versus transplantation after one year on dialysis was 37 (95% CI: 12 - 62) and 41 (95% CI: 14 - 69) for DD and LD kidney recipients respectively, whereas it was 54 (95% CI: 16 - 92) and 60 (95% CI: 20 - 100) in 1998. The NNT with pre-emptive transplantation versus after two years dialysis was 25 (95% CI: 10 - 40) and 27 (95% CI: 11 - 42) in 1988 compared to 41 (95% CI: 15 - 65) and 42 (95% CI: 18 - 66) in 1998 for DD and LD transplants respectively.

Sensitivity analysis

All analyses were repeated within a subcohort of 1978 patients who had a primary renal disease which is not known for recurrence in a kidney allograft. All results were similar to those described above (data not shown).

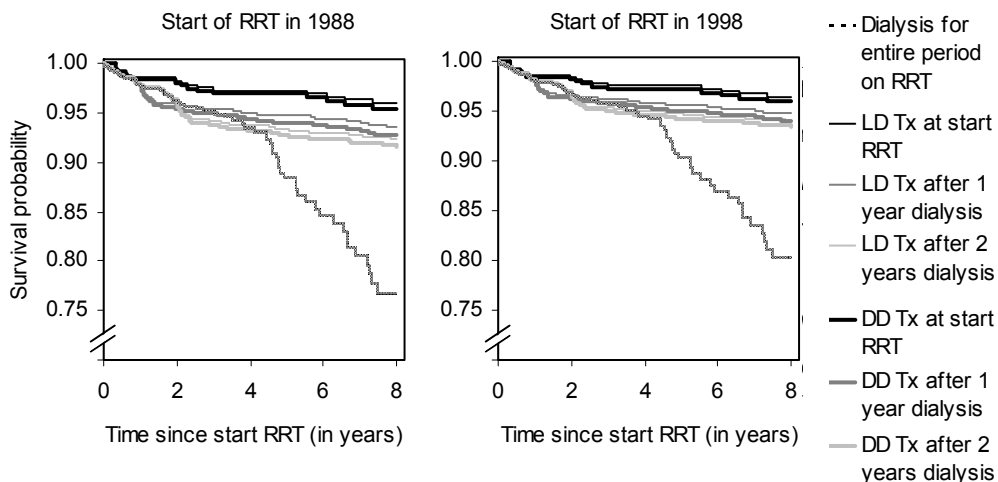


	two-year survival	five-year survival	eight-year survival
On dialysis for entire period on RRT	97.7 (96.3 - 99.1)	93.1 (88.9 - 97.4)	85.7 (77.8 - 94.3)
Deceased donor kidney transplantation			
pre-emptive	98.0 (95.9 - 100)	96.8 (93.6 - 100)	95.3 (90.9 - 99.9)
after one year on dialysis	96.4 (94.9 - 97.9)	94.9 (93.0 - 96.9)	93.7 (91.3 - 96.1)
after two years on dialysis	97.7 (96.3 - 99.1)	94.6 (92.5 - 96.7)	93.4 (91.0 - 95.9)
Living donor kidney transplantation			
pre-emptive	98.3 (96.8 - 99.8)	97.2 (95.1 - 99.4)	95.9 (93.1 - 98.8)
after one year on dialysis	96.8 (95.3 - 98.3)	95.6 (93.5 - 97.7)	94.5 (91.9 - 97.2)
after two years on dialysis	97.7 (96.3 - 99.1)	95.1 (93.0 - 97.3)	94.2 (91.6 - 96.8)

Figure 2. Simulated patient survival curves for averaged values of age (13.02), period (1995.2), gender (42% female), and primary renal disease (glomerulonephritis=12%, pyelonephritis=21%, cystic kidneys=10%, hypoplasia / dysplasia=15%, hereditary nephropathy=11% and other PRD=31%), stratified by donor source.

Questionnaire

The questionnaire on how frequently kidney transplantation was denied or delayed, and on the characteristics of the children who had this experience was completed by nine out of the ten paediatric nephrologists invited. All participants indicated that low weight and/or a very young age were reasons to delay transplantation in children. Other reasons to postpone transplantation, in order of decreasing frequency were malignancies, recurrent diseases, teenager non-compliance, and neurological diseases. Seven paediatric nephrologists reported that in less than 5% of the cases children were considered unsuitable for transplantation, while the remaining two reported that in their countries children were never considered unsuitable for transplantation. Reasons for withholding transplantation were malignancies, severe recurrent diseases and neurological diseases.



	two-year survival	five-year survival	eight-year survival
Start of RRT in 1988			
On dialysis for entire period on RRT	96.1 (93.6 - 98.8)	88.6 (81.3 - 96.4)	76.9 (64.1 - 92.3)
Deceased donor kidney transplantation			
pre-emptive	98.1 (95.8 - 100)	97.0 (93.6 - 100)	95.5 (90.7 - 100)
after one year on dialysis	95.5 (93.4 - 97.7)	94.1 (91.4 - 96.9)	92.8 (89.5 - 96.2)
after two years on dialysis	96.1 (93.6 - 98.8)	92.8 (89.7 - 96.0)	91.6 (88.1 - 95.1)
Living donor kidney transplantation			
pre-emptive	98.4 (96.7 - 100)	97.4 (94.9 - 99.9)	96.1 (92.7 - 99.6)
after one year on dialysis	96.0 (93.9 - 98.1)	94.7 (92.1 - 97.5)	93.7 (90.4 - 97.1)
after two years on dialysis	96.1 (93.6 - 98.8)	93.4 (90.2 - 96.6)	92.4 (88.9 - 96.0)
Start of RRT in 1998			
On dialysis for entire period on RRT	96.8 (95.0 - 98.6)	90.4 (85.3 - 95.8)	80.4 (70.7 - 91.4)
Deceased donor kidney transplantation			
pre-emptive	98.3 (96.5 - 100)	97.3 (94.6 - 100)	96.0 (92.3 - 99.8)
after one year on dialysis	96.4 (94.9 - 97.8)	95.2 (93.3 - 97.1)	94.1 (91.9 - 96.4)
after two years on dialysis	96.8 (95.0 - 98.6)	94.4 (92.1 - 96.7)	93.5 (90.9 - 96.1)
Living donor kidney transplantation			
pre-emptive	98.5 (97.3 - 99.8)	97.6 (95.9 - 99.4)	96.5 (94.1 - 98.9)
after one year on dialysis	96.7 (95.2 - 98.2)	95.7 (93.8 - 97.6)	94.8 (92.5 - 97.2)
after two years on dialysis	96.8 (95.0 - 98.6)	94.8 (92.5 - 97.1)	94.0 (91.5 - 96.6)

Figure 3. Simulated patient survival curves for averaged values of age (13.02), gender (42% female), and primary renal disease (glomerulonephritis=12%, pyelonephritis=21%, cystic kidneys=10%, hypoplasia / dysplasia=15%, hereditary nephropathy=11% and other PRD=31%), stratified by donor source and year in which RRT was initiated.

Discussion

This is the first study to examine the influence of the timing of the first kidney transplant in children, while including patients from the start of RRT. As a result for the first time it was possible to account for the mortality during the waiting time on dialysis before transplantation. As the far majority of the children had received a transplant within two years, treatment scenarios were developed in which children underwent PKT or transplantation after one or two years on dialysis (post dialysis transplantation (PDT)). For each of the treatment scenarios, survival curves were simulated based on patient data from 2091 children who started RRT below the age of 18 years between 1988 and 2007. As this study examined the influence of decision-making at the start of RRT we took an intention-to-treat approach.

Our results showed that the survival of children who received a transplant (either pre-emptive or preceded by dialysis) was substantially better than of those remaining on dialysis, which is likely a combination of transplantation being the better treatment option for children and of patient selection. In addition, in both LD and DD kidney recipients the data suggested a minor survival benefit for PKT when compared to patients who were on dialysis for one or two years before transplantation, but this difference was not statistically significant. However, the survival disadvantage of postponing transplantation increased per additional year spent on dialysis before transplantation. The 8-year patient survival of a child transplanted pre-emptively was 1.9% (95% CI: -3.2 to 7.0) higher for DD transplants and 1.7% (95% CI: -2.1 to 5.6) higher for LD transplants compared to a child transplanted after two years on dialysis. The simulated survival curves for patients starting RRT in 1988 or in 1998 showed similar results with regard to the different treatment scenarios. However, the potential eight-year survival disadvantage resulting from one additional year on dialysis before transplantation decreased during this decade. This was due to the improvement in survival of patients on dialysis in absolute terms during this period (by 3.5% for eight-year survival, see table beneath Figure 3). This improvement provided children waiting for a transplant with a better chance of survival up to the moment of their transplant.

As the results of the questionnaire indicated that low weight and/or a very young age were reasons to delay transplantation in children, we excluded from the analyses all patients younger than three years of age at the start of RRT. However, literature has shown that children younger than two years of age at the start of RRT have similar patient survival after transplantation [26,26,27,27,28,28] but a worse patient survival after starting dialysis [29] when compared to children older than two years of age at the start of RRT. The exclusion of patients younger than three years of age from our analyses may have resulted in an underestimation of the negative effect of postponing transplantation on the patient survival

within the entire paediatric population. Therefore, we would like to stress that our results are only generalizable to patients older than three years and younger than eighteen years of age at the start of RRT.

Many studies have investigated the effect of pre-emptive transplantation as predictor for *graft* survival after kidney transplantation in children [12-14,30-32]. One of these studies reported better graft survival for PKT in LD kidney recipients [31], two others also found a graft survival benefit for PKT in LD kidney recipients, but not in DD kidney recipients [13,32] and the remaining three reported no difference in graft survival between PKT and PDT in LD and DD kidney recipients together [12,14,30]. All these studies [12-14,30-32] only included children after they had actually received a kidney transplant and, therefore, only examined the survival from the time of transplantation. This means that the deaths of patients who were on dialysis while they were waiting for a kidney transplant were not taken into account thereby underestimating a potential difference and biasing the results in favour of transplantation after a period of dialysis. Two of these studies [12,13] also examined the influence of dialysis prior to transplantation as predictor variable (i.e. pre-emptive yes/no) on the *patient* survival in children. In these studies PDT results only include survival of those who made it up to transplantation. Vats et al. [13] reported on 2495 children in the North American Paediatric Renal Transplant Cooperative Study (NAPRTCS) registry who underwent LD or DD kidney transplantation between 1992 and 1996 pre-emptively or after a period of haemodialysis or peritoneal dialysis. They found that patient survival rates did not differ between PKT and PDT. Tangeraas et al. [12] studied the patient survival of 251 children who received a kidney transplant (both from LD and DD kidney recipients) between 1970 and 2006 but found no statistically significant difference between PKT and PDT. Our study is the only one taking into account the mortality on dialysis before transplantation by including children from the start of RRT (and not from the start of (post-dialysis) kidney transplantation). Assessment of this early mortality on dialysis and including it in the analysis are needed for a fair comparison of survival from the start of RRT between PKT and PDT.

Some potential limitations of this study need to be considered. Firstly, this large study including data from 2091 children and 138 events (deaths) potentially still lacked power to detect a real difference in patient survival. However, if there is a difference in patient survival between children transplanted pre-emptively and children transplanted after a short period on dialysis, it is likely to be relatively small and decreasing due to a secular trend of improved survival on dialysis during the study period.

Secondly, children who are suitable for kidney transplantation could be different from children who remain on dialysis. Wolfe et al. [33], for example, showed that adult patients placed on the waiting list for kidney transplantation were healthier and that their survival was superior to that of patients on dialysis who were not put on the waiting list. In children, this

'confounding by indication' is likely to be small as nephrologists from participating countries estimated that only in less than 5% of the cases children are considered unsuitable for transplantation. In addition, most of the children less suitable for transplantation (those younger than 3 years of age and those with kidney tumours or haemolytic uraemic syndrome) were excluded from the analysis, whereas in- or exclusion of recurrent disease did not affect our findings. Nevertheless, even if this measure did not completely prevent 'confounding by indication', our estimation of the potential 8-year survival benefit of pre-emptive transplantation compared to transplantation after two years (1.9% (95% CI: -3.2 ; 7.0) for DD transplants and 1.7% (95% CI: -2.1 ; 5.6) for LD transplants) would still be an overestimation and a real difference would be smaller. After all, in our model, the survival estimated for the time on dialysis was based on all patients including the potentially less healthy ones, giving the patients on dialysis (but suitable for transplantation) an artificially worse prognosis for their time on dialysis.

In addition, it has been shown that children who are transplanted pre-emptively (independent of donor source) had higher levels of estimated glomerular filtration rate at the start of RRT than patients who started RRT with dialysis [34]. This suggests that patients with a pre-emptive kidney transplant started RRT earlier than dialysis patients, which will increase the estimated survival of this first group because of lead time bias. Again, this lead time bias might have resulted in an overestimation of the potential survival advantage of patients receiving a transplant pre-emptively compared to those receiving one after a period on dialysis and a real difference would be smaller.

Finally, this study could only examine the outcome of patient survival, whereas we know that in the decision whether or not to transplant pre-emptively also other factors outside of the scope of this study will be considered important. Factors such as quality of life and growth will also be taken into consideration, since dialysis is associated with both poorer growth [35] and a poorer quality of life (for both the patient and his family) [36,37] than transplantation. A further advantage of performing PKT is that the child's available dialysis access sites will be preserved. These are all factors in favour of pre-emptive transplantation. On the other hand, if a period on dialysis may allow receipt of a better matched donor kidney, long-term outcomes of the first as well as subsequent transplants may be improved [38] Moreover, donor and recipient preparation for kidney transplantation takes several months [39] and this time may not always be available. In the latter context the knowledge gained from this study may not be critical for nephrologists' decision-making but may still be information of some re-assurance for parents who fear that not providing a renal allograft right away will importantly decrease the life expectancy of their child.

We conclude that, from the perspective of patient survival, pre-emptive kidney transplantation is potentially preferable to starting RRT with dialysis, although any survival differences with starting RRT by a short period on dialysis are likely to be small. Judgement

of the optimal timing of transplantation should be individualized considering additional advantages of pre-emptive kidney transplantation such as improved growth and quality of life. However, if starting with a pre-emptive transplant raises substantial problems, for example when a child is not referred in a timely manner to the nephrologist, transplantation after a short period of dialysis may be an acceptable alternative, as it is not expected to substantially decrease the child's survival prospects.

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