European disparities in the incidence and outcomes of children with end-stage renal disease

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Survival in children requiring chronic renal replacement therapy

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ABSTRACT

Survival in the paediatric end-stage renal disease (ESRD) population has improved substantially over the past decades. Nonetheless, mortality remains at least 30 times higher than that of healthy peers. Patient survival is multifactorial, dependent on various patient and treatment characteristics, as well as on the degree of economic welfare of the country in which a patient is treated. In this educational review we aim to delineate the current evidence regarding mortality risk in the paediatric ESRD population, and provide paediatric nephrologists with an up-to-date knowledge base required to counsel affected families.

INTRODUCTION

Approximately 9 out of every million children under 20 years of age in the developed world require renal replacement therapy (RRT) for the treatment of end-stage renal disease (ESRD) [5]. Mortality risk in these children is multifactorial, owing to the complex nature and multiple causes of ESRD in this population, and is at least 30 times higher than that of healthy peers [79, 107]. Although other patient-related outcomes such as growth, psychosocial development and quality-of-life are of major importance, prolongation of patient survival may be arguably the most relevant clinical goal. As ESRD in children is a rare condition, the statistical power needed to accurately assess (risk factors related to) survival has been limited. Over the past years, various (inter)national registries have been instrumental in providing sufficient data to advance epidemiological research, and expand the evidence regarding outcomes and treatment guidelines for this population. In this review, we aim to delineate the current evidence base regarding mortality risk in the paediatric RRT population, and provide paediatric nephrologists with up-to-date data to counsel affected families.

IMPROVEMENTS IN PATIENT SURVIVAL

Since the introduction of the first paediatric chronic RRT programs during the 1960s, substantial advances in renal medicine have been achieved (Box 1) [108, 109], and survival has improved significantly, especially in the youngest patients. Historic registry data from Australia and New Zealand (ANZDATA registry) cite a 10-year mortality rate of 110 deaths per 1000 patient years during the 1960s, which was halved with each subsequent decade, stabilizing at 18 deaths per 1000 patient years during the 90s [8]. In European dialysis patients, the 5-year mortality risk decreased by 36% from 1980-1984 to 1995-2000, and by 79% in the subgroup of patients aged 0-4 years [68]. In the US, dialysis survival improved during 1990-2010, with each 5-year increment decreasing mortality by 12% decrease in children over 5 years of age, and by 20% in children under 5 years [34]. In neonates and infants initiating dialysis, the majority now survive long enough on dialysis to reach the minimum age and body weight required for successful transplantation [86, 110].

Post-transplant survival has also improved over time. The mortality risk in European first renal transplant recipients decreased by 42% for the period 1995-2000 compared with 1980-1984 [68]. Between 1990-2010 in the US, each additional calendar year led to a 3% decrease in mortality risk, which was 5% for children under 5 years of age. Improvements were most pronounced during the first year post-transplant [111]. The 5-year survival for deceased donor recipients improved from 91.2% during 1987-1995 to 96.4% during 2005-2013, and from 95.1% to 97.1% for living donor recipients [11].

Presently, the overall 5-year survival for paediatric RRT patients is approximately 90%, and is similar across high-income countries (Table 1). In Europe, survival currently ranges from 82% to 96% at 10 years, and from 76% to 89% at 20 years. Long-term survival probabilities for European patients are presented by age group and initial treatment modality in table 2 (personal communication; Anneke Kramer, 25 January 2017).

Box 1. Key developments in paediatric renal medicine

The introduction of continuous ambulatory peritoneal dialysis [100]
The development of haemodiafiltration [101]
The development of home HD programs [102]
The introduction of portable PD devices [103]
Improvements in pre-dialysis care [104]
Introduction of the "Y-set" catheter connection for PD [105]
The use of bicarbonate-buffer for dialysis [106]
The addition of amino acids to dialysate [107]
The development of erythropoietin [108]
The development of growth hormone therapy [109]
An increased percentage of pre-emptive Tx [90]
Innovation of immunosuppressive drugs [110]
Improvements in nutrition [111]

Table 1. Five-year crude survival probabilities of paediatric RRT patients by country and period [35, 62, 66, 79, 112, 113]. [1] Four-year survival probability; [2] Incident dialysis patients only.

Country/Area	*Period*	*Survival*
Australia and New Zealand	1963-2002	83%
United States	2004-2008	89%
Canada	1992-2007	92%
Europe[1]	2009-2011	94%
Japan	2006-2011	92%
Taiwan[2]	1995-2004	88%

Table 2. Long-term crude survival for patients initiating RRT between 1990 and 2014 by age group and initial treatment modality, using European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) data for the countries Austria, Bosnia and Herzegovina, Denmark, Spain, Finland, France, Greece, Iceland, The Netherlands, Norway, Romania, Serbia, Sweden, and Scotland (personal communication; Anneke Kramer, 25 January 2017). HD = haemodialysis, PD = peritoneal dialysis, Tx = transplantation.

	5-yr	*10-yr*	*15-yr*	*20-yr*
Overall	94%	90%	87%	83%
Age				
0-1	85%	82%	79%	76%
2-5	92%	88%	83%	81%
6-12	95%	93%	90%	85%
13-18	95%	92%	88%	85%
First RRT modality				
HD	94%	90%	86%	82%
PD	92%	88%	85%	82%
Tx	97%	96%	93%	89%

FACTORS ASSOCIATED WITH MORTALITY

Age

Age at dialysis initiation is a key determinant of patient survival. Registry data has consistently shown that, compared with adolescents, mortality risk is approximately 4 times higher in children < 5 years of age at dialysis initiation, and 1.5 times higher in children aged > 5 years of age [8, 34, 79, 114]. Mortality risk remains the highest in neonatal and infant dialysis patients [114, 115], whom are technically challenging to treat due to small body size, a high risk of infection, difficulties in nutrition and growth, and a high prevalence of (severe) comorbidities [116, 117]. These challenges and a perceived unacceptable quality of life form important factors in the decision to withhold or withdraw treatment in some of these children [117–120]. Moreover, transplantation is often not feasible due to the small size of the child relative to the large donor kidney, and is usually recommended after reaching a minimum of 18 months of age or a weight of 10 kg. Growth retardation, which is highly prevalent in these children, delays reaching the recommended transplant weight/age, thus further delaying transplantation and increasing time on dialysis, which in turn increases the mortality risk in this already vulnerable population [117, 121]. Nonetheless, relatively good clinical outcomes have been reported and survival has improved significantly in this group. An international collaboration recently demonstrated a 5-year survival of 76% and a transplant probability of 55%, concluding that relatively good survival may be achieved in neonates, despite the high prevalence (73%) of comorbidities [86].

Sex

No studies have specifically investigated a possible effect of sex on mortality in the paediatric ESRD population, but girls seem to have a higher mortality risk than boys [107]. In the US, girls over the age of 5 on dialysis had a 27% increased mortality risk compared with boys, although this effect was less pronounced in younger children [34]. In the US transplant population, girls had a 18% higher cardiovascular-related and an 37% higher infection-related mortality risk compared with boys [36]. A potential explanation was suggested by a European study demonstrating a 23% decreased probability of pre-emptive transplantation in girls compared with boys. This disparity was mostly explained by the fact that girls tended to progress faster to ESRD compared with boys and by differences in age and primary renal

disease distribution. Other potential non-medical factors such as patient, parental, and physician attitudes towards transplantation may also play a role [122].

Race

Patient race has also been shown to affect mortality risk in the paediatric RRT population. In the US, black race was associated with a 25% higher risk of death compared with white race in first transplant recipients [123], and a 64% higher risk of death in dialysis patients. The likelihood of transplantation was also lower in both black and Hispanic dialysis patients [124]. Furthermore, black children were 1.6 times more likely to die from cardiovascular causes before the age of 30 compared with white children [125]. The former has been attributed to a higher incidence of hypertension, arrhythmia, cardiomyopathy, and valvular heart disease in black patients [126, 127]. Also in CKD stages 1-3, black children were more likely to have elevated systolic and diastolic blood pressure compared with non-black children [128]. In Europe, black and Asian patients were less likely to receive a transplant, and Asian patients had a 2.5-fold higher mortality risk compared with white patients [129]. The latter was reduced after adjustment for primary renal disease, suggesting that differences in renal disease distribution between races explains a part of these disparities.

Primary renal disease

Congenital anomalies of the kidney and urinary tract (CAKUT) and glomerulonephritis form the most common aetiologies of renal disease in children, accounting for at least half of all paediatric ESRD patients [79, 113]. Patients suffering from CAKUT have the best survival probabilities of all primary renal disease groups, although survival varies by aetiology [34, 115, 130]. In infants and neonates, those with renal hypo/dysplasia, congenital nephrotic syndrome, polycystic disease, and other/unknown had a 2 to 4 times increased mortality risk compared with those with obstructive uropathy [110]. Poor patient survival has also been described in patients with secondary glomerulonephritis, vasculitis, systemic lupus erythematosus, and primary hyperoxaluria [130–132].

Anthropometry

Children that are either underweight or obese at ESRD onset have an increased mortality risk. In the US, this U-shaped association was demonstrated in both dialysis and transplant patients, with mortality risk increasing by 26% for every 2 SD increase or decrease from the 0.5 BMI SDS reference value [133]. In children with a high BMI, volume overload, edema, or comorbidity may explain the increased mortality risk. In underweight children, disease severity and malnutrition may be accountable. Low serum albumin (<3.5 g/dL), a marker for malnutrition or inflammation, was indeed associated with a 90% increased risk of death [33]. Similarly, Ku et al. found that both obese (17% increase) and underweight (26% increase) children were at increased risk of mortality. Interestingly, they found that obese children were less likely to receive a transplant especially from a living donor, and that this attenuated their increased mortality risk [134].

Growth failure in the paediatric RRT population may reflect disease severity and is associated with increased mortality [135]. In the US, every SDS decrease in height increased mortality risk by 14%. This effect was particularly evident in children under 14 years of age, but was similar across treatment modalities [133]. A NAPRTCS study echoed these results, demonstrating that mortality risk was twice as high in children initiating dialysis with a height SDS of less than 2.5 compared with children with a normal height [136]. More recently in the US, both short (<3rd percentile) and tall (>3rd percentile) stature at RRT initiation were associated with an increased risk of death compared with less extreme heights, although the latter was limited to a small group of children with an elevated BMI (>95th percentile) and white race [137].

Comorbidity

Extra-renal comorbidity is common in the paediatric ESRD population. The UK Renal Registry reported that at the onset of RRT in 2009-2013, 19.3% of paediatric patients had at least one comorbidity, and 9.5% had two or more comorbidities. Syndromic diagnosis (8%), developmental delay (7%), and congenital abnormality (7%) were the most frequently reported comorbidities [138]. Multiple studies have shown that the presence of comorbidity is an important predictor of mortality [34, 139], especially in patients with cognitive (5-year survival probability of 63%), cardiac (73%), and pulmonary (50%) abnormalities [140]. In a single-centre

study from the UK, 76% of the dialysis patients who died had a comorbid condition, resulting in a 7.5 times increased mortality compared with those without comorbidities [141]. Several studies have shown that particularly the youngest patients with co-morbid conditions have an increased mortality risk, especially those with pulmonary hypoplasia [142–145].

RRT modality

It has been well established that (pre-emptive) renal transplantation offers better survival probabilities compared with dialysis [8, 146]. Nonetheless, approximately 80% of paediatric patients will initiate RRT on dialysis to bridge the preparation time needed for transplantation, or will require dialysis after graft loss [79]. Survival comparisons by dialysis modality in a randomized clinical trial (RCT) setting have proved extremely difficult [147]. Consequently, survival comparisons remain reliant on observational studies [33–35, 148–150]. In adults, there seems to be a consistent trend showing a survival advantage during the first few years on PD, especially in younger, healthier, and non-diabetic patients [27–32, 151]. In the paediatric dialysis population, recent registry data from Europe and the US demonstrate a 21%-32% reduced mortality risk in children initiating dialysis on PD [34, 148, 149]. In the US, this treatment effect was only present in children younger than 5 years of age, whereas in Europe this effect was less pronounced in children younger than 5 years and absent in infants [34, 148]. Furthermore, European data show that this treatment effect was stronger during the first year of dialysis, in older children, and in those with a short time under treatment of a nephrologist prior to starting dialysis (figure 1). As the latter may serve as a proxy for timely referral and the speed of disease progression, this may prelude to indication bias due to unmeasured case-mix confounders, as sicker patients are more likely selected to start dialysis on HD [148].

Time on RRT

Time spent on dialysis has been shown to impact mortality risk, which is highest during the first year of treatment, and reflects the intrinsic mortality risk of initiating dialysis. In the US, mortality rates reach 48 per 1000 patient years during the first month, peak during the second month of dialysis at 57, then slowly decrease to 28 during months 9-12. Rates of mortality due to cardiovascular disease and infection show similar patterns [152].

The duration of living with a functioning graft has been shown to decrease patient mortality risk. In the US, in first transplant recipients, mortality was highest during the first post-transplant year, after which mortality risk decreased (albeit not significantly) by 1% for each additional follow-up year. This effect was stronger for cardiovascular-specific mortality, which decreased by 16% for each follow-up year, suggesting that transplantation has no cumulative negative effect on the cardiovascular health in young recipients. However, returning to dialysis after graft failure was associated with a 4.4-fold increase in overall mortality risk and a 7.8-fold increase in cardiovascular mortality risk [36].

Residual renal function

In adult dialysis patients, a decrease in residual renal function has been associated with an increase in mortality risk [153, 154]. Data is lacking in the paediatric population. Two single-centre US studies demonstrated that infants with oligoanuria had a higher mortality risk compared with infants with residual renal function [144, 145], and others have demonstrated a positive effect of residual renal function on growth and nutrition [155–157].

GFR at RRT initiation

The literature discussing the relationship between GFR at dialysis initiation and mortality risk in adults is conflicting [158–160], and this question has not yet been studied in children, although a study from the US found that children with a higher GFR at dialysis initiation had a decreased risk of hospitalization for hypertension and pulmonary edema [161]. A single RCT has tackled this question in adults, finding no difference in survival between late and early starters, although the difference (2.2 ml/min/1.73m^2) in GFR between groups was smaller than anticipated. Nonetheless, dialysis initiation was delayed by 6 months amongst the late starters, which is favourable for both patients and costs [162].

CAUSES OF DEATH

Cardiovascular disease and infection-related mortality

Cardiovascular disease (CVD) and infection-related mortality are the major causes of death in the paediatric RRT population, accountable for approximately 30% and 20% of deaths, respectively, although these rates vary strongly by country, age, race, the definition used, and treatment modality [70, 79, 125, 152]. In Europe, infections were the leading cause of death in those on PD and those with a functioning graft, whereas cardiovascular causes of death dominated in patients on HD [79]. In the US, a 4.5 times increased risk of CVD death in dialysis patients compared with transplant recipients has been reported [125]. An increased CVD mortality risk for dialysis patients was also cited in Australia and New Zealand, where between 1963-2002, CVD death accounted for 57% of deaths in children on HD, 43% in children on PD, but only for 30% in those with a functioning transplant [8]. Both CVD and infection-related mortality have decreased over the past decades in the US [34]. Vogelzang et al. studied changes in causes of death in adults after long-term RRT since childhood in the Netherlands, finding that CVD mortality risk had decreased by 91% since the 70s, whereas infection-related mortality risk had doubled over time. The decrease in CVD mortality was attributed to an increased awareness amongst nephrologists of the burden of cardiovascular disease and a subsequent strict cardiovascular management in these patients [69].

Malignancy-related mortality

Malignancy-related death occurs more often in transplant recipients compared with those on dialysis, and is likely caused by an impaired tumour immune surveillance due to immunosuppression [36, 107, 163–165]. In Australia and New Zealand, malignancies accounted for 14% of deaths among transplant recipients, compared with only 1% and 2% percent of deaths among patients on HD and PD, respectively, with most deaths occurring after 10 years of RRT [8]. Furthermore, paediatric transplant recipients had a 15-30 times increased risk of developing a malignancy compared with the general population [166]. In the Netherlands, 30 years after paediatric transplantation, 41% of survivors had developed cancer, and 31% had developed a second de novo cancer during the first year after initial diagnosis. Malignancies were responsible for 13% of all deaths in the cohort. The overall incidence of malignancy was more than 20-fold higher compared with the general population with a notable increase in risk starting after 20 years of follow-up [167].

INTERNATIONAL DISPARITIES IN SURVIVAL

As economic welfare is a key determinant of health and access to health services, in low and middle income countries the provision of chronic RRT is fraught with challenges. The complexity and cost involved in the provision of renal care to children, a lack of financial and human resources, different health priorities, and an inadequate health infrastructure have obvious consequences for access to RRT and the survival probabilities of patients in these countries [168, 169]. In 2010, at least half of the 4.9 million people requiring RRT worldwide died prematurely because they did not have access to treatment [3]. Specifically in children, it has been suggested that possibly no more than 10% of those requiring RRT have access to treatment, and that most of these preventable deaths occurred in low- and middle- income countries [170]. The few studies available in lower-income countries, where renal registries are often lacking, confirm these disparities. In Jamaica, between 2001-2006, of all ESRD patients under 12 years of age at diagnosis, 62.5% died due to restricted access to RRT [171]. In a tertiary hospital in South-West Nigeria, between 2005 and 2012, the median survival time of 51 admitted paediatric ESRD patients was only 47 days. Of these, 82% had received an acute dose of dialysis, however, continuation of RRT was not possible due to financial constraints, likely resulting in death shortly after discharge [172]. In two tertiary hospitals in Vietnam, between 2001 and 2005, only 27% of admitted paediatric ESRD patients received RRT. The remainder were treated conservatively due to a lack of financial resources [173]. In a tertiary care hospital in India, 61% of admitted paediatric ESRD patients were either treated conservatively or opted against further treatment due to the high cost of RRT, likely resulting in death [174]. As only a fraction of children requiring RRT globally actually receive treatment, and an equitable and universal provision of costly RRT is unrealistic in the short term, the largest gains in survival are likely to be made by delaying progression of CKD and preventing ESRD [168, 175].

Even amongst high- and middle-income countries, survival probabilities of paediatric RRT may vary. We recently demonstrated that considerable international variation exists in mortality rates across Europe, mostly attributable to an excess mortality risk for patients treated in several Eastern European countries. Most of this variation was explained by disparities in country public health expenditure, which limits the availability and quality of paediatric renal care services. In addition, differences in a country's ability to accept and successfully treat the

youngest children, who are the most complex and costly to treat, formed an additional source of disparity within Europe. Economic constraints in Europe were also associated with a lower incidence of RRT [93]. As non-acceptance to RRT implies an underestimation of ESRD mortality (as these deaths go unregistered), the inequalities in mortality caused by economic constraints will be exacerbated. In addition, considerable country variation persists in transplant rates, donor source, and time on the transplant waiting list which, given the beneficial effect of transplantation, will affect patient survival indirectly [42].

RECOMMENDATIONS FOR LONG-TERM FOLLOW-UP THROUGH ADULT LIFE

The increased mortality risk of paediatric onset ESRD carries on through adulthood, with life expectancy reduced by 40–50 years in dialysis patients and by 20–30 years in transplant patients [176]. Cardiovascular disease is highly prevalent amongst young adults after a lengthy exposure to RRT, but has been shown to be reversible [177–180]. Strict monitoring of cardiovascular disease, and intensified antihypertensive and antilipaemic therapy should therefore be a priority in this population. Furthermore, as the majority of paediatric onset ESRD patients will have received a transplant prior to transitioning to adult care, continued compliance to immunosuppression regimens is of the upmost importance, especially given that up to 53% of adolescents have been reported to be non-compliant [181–183]. Moreover, due to prolonged exposure to immunosuppression in these patients, adult nephrologists should be attentive to the increased risk of infections, and the development of skin cancers 10-15 years post-transplantation.

KNOWLEDGE GAPS

National and international registries for paediatric RRT have been instrumental in describing survival and establishing factors associated with mortality in this population. However, data from middle- and lower-income countries remain scarce. The forthcoming IPNA Registry aims to consolidate existing registry data and fill in the gaps by collecting data globally [184]. Worldwide reporting of paediatric RRT is essential in order to reveal international disparities regarding treatment and mortality rates, increase the awareness regarding these disparities in the paediatric nephrology community, and provide the evidence required to advocate policy change and inform budgetary decisions on various levels of government.

Furthermore, although associations between mortality and various patient and treatment related factors have been studied in the adult RRT population, simple extrapolation of these results to children is often not valid given the differences in disease aetiology and progression. Small samples sizes and a low number of adverse events often impede epidemiological research in the paediatric RRT population. Nonetheless, with continued support and commitment, the volume of registry data will increase over time, hopefully enabling studies to fill in the knowledge gaps concerning the determinants of mortality, specifically in the paediatric RRT population [185].

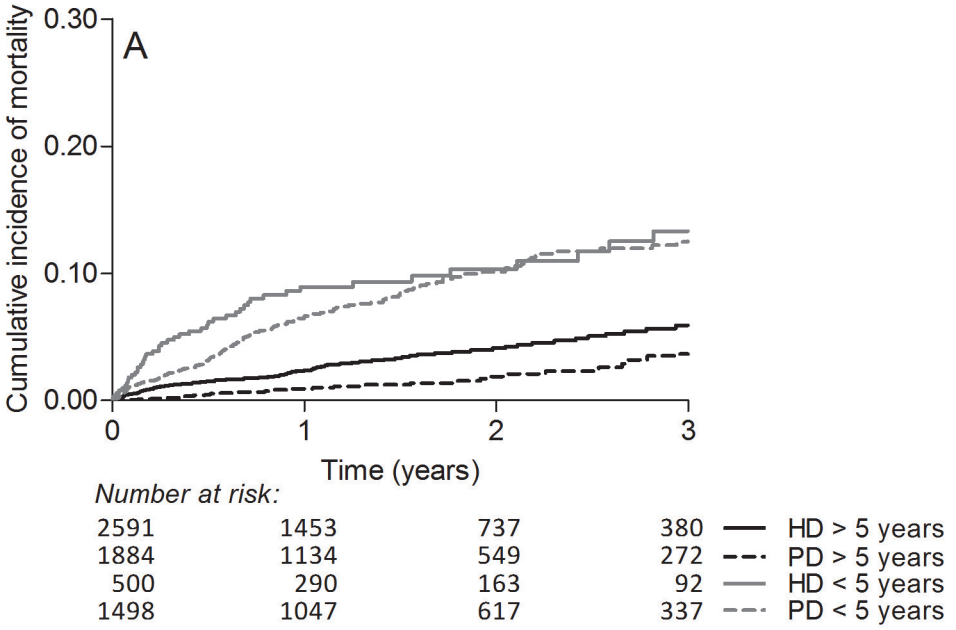
LIMITATIONS

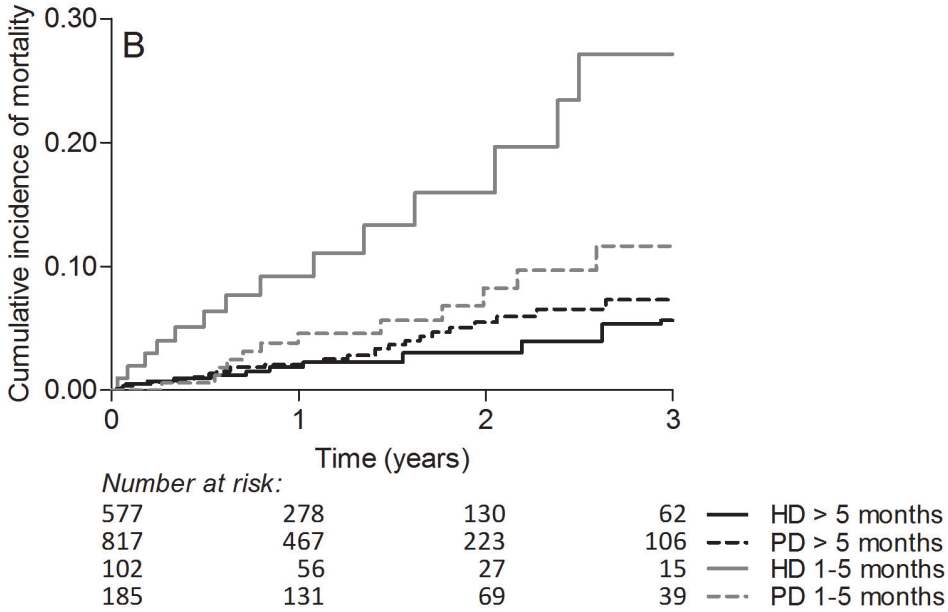
Several factors limited our ability to investigate the mortality risk in the paediatric RRT population. First, children with ESRD who are not accepted on RRT, or died prior to treatment initiation, are not registered. Second, in registries patients are frequently lost to follow-up when transferred to adult care, precluding registration of premature death during (early) adulthood, and thirdly, studies often focus on mortality risk on either dialysis or transplantation instead of throughout the entire RRT trajectory. Lastly, in contrast to adult patients, virtually all children with ESRD are considered transplantable. Consequently, long-term dialysis studies are scarce and subject to negative selection of non-transplantable patients.

SUMMARY

Patient survival has improved substantially over the past decades in both the paediatric dialysis and transplant population, especially in the youngest patients. First and foremost, as global disparities persist in the provision of paediatric renal care, patient survival is primarily dependent on access to treatment. In patients receiving RRT, survival is largely dependent on country health expenditure, disease aetiology, patient age, transplant feasibility, growth failure, sex, BMI, race, and the presence of comorbidities.

Figure 1. Cumulative incidence plots by dialysis modality and A) age group at the start of renal replacement therapy, and B) the time under treatment by a nephrologist. Reproduced with minor modification and permission from Kidney International [148]. HD = haemodialysis, PD = peritoneal dialysis.





SUMMARY BOX

- Patient survival has improved substantially over the past decades in both the dialysis and transplant population, and although the youngest patients bear the highest mortality risk, they also show the greatest improvement in survival over time.
- Patient survival is multifactorial, largely dependent on access to treatment, country health expenditure, disease aetiology, patient age, transplant feasibility, growth failure, sex, BMI, race, and the presence of comorbidities.
- Although comparisons between dialysis modalities are hindered by selection bias and residual confounding, patients selected to start dialysis on PD seem to have an initial survival advantage over those starting on HD.
- Global disparities persist in the provision of RRT and outcomes in the paediatric ESRD population, even amongst middle- and higher income countries.