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ORIGINAL ARTICLE

# Adult outcomes of childhood kidney replacement therapy in Europe from 2008 to 2019: an ERA Registry study

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## ABSTRACT

**Background.** Young adults starting kidney replacement therapy (KRT) during childhood and reaching their 18th birthday (i.e. adult survivors of childhood KRT) form a challenging population of interest to nephrologists treating adults, as during this period there will be a transition to adult renal centres. Nonetheless, few studies have focused on the epidemiology of KRT in this group. We aimed to provide an update on these patients' characteristics, treatment history, and graft and patient survival, to report their 5-year prognosis and expected remaining lifetime.

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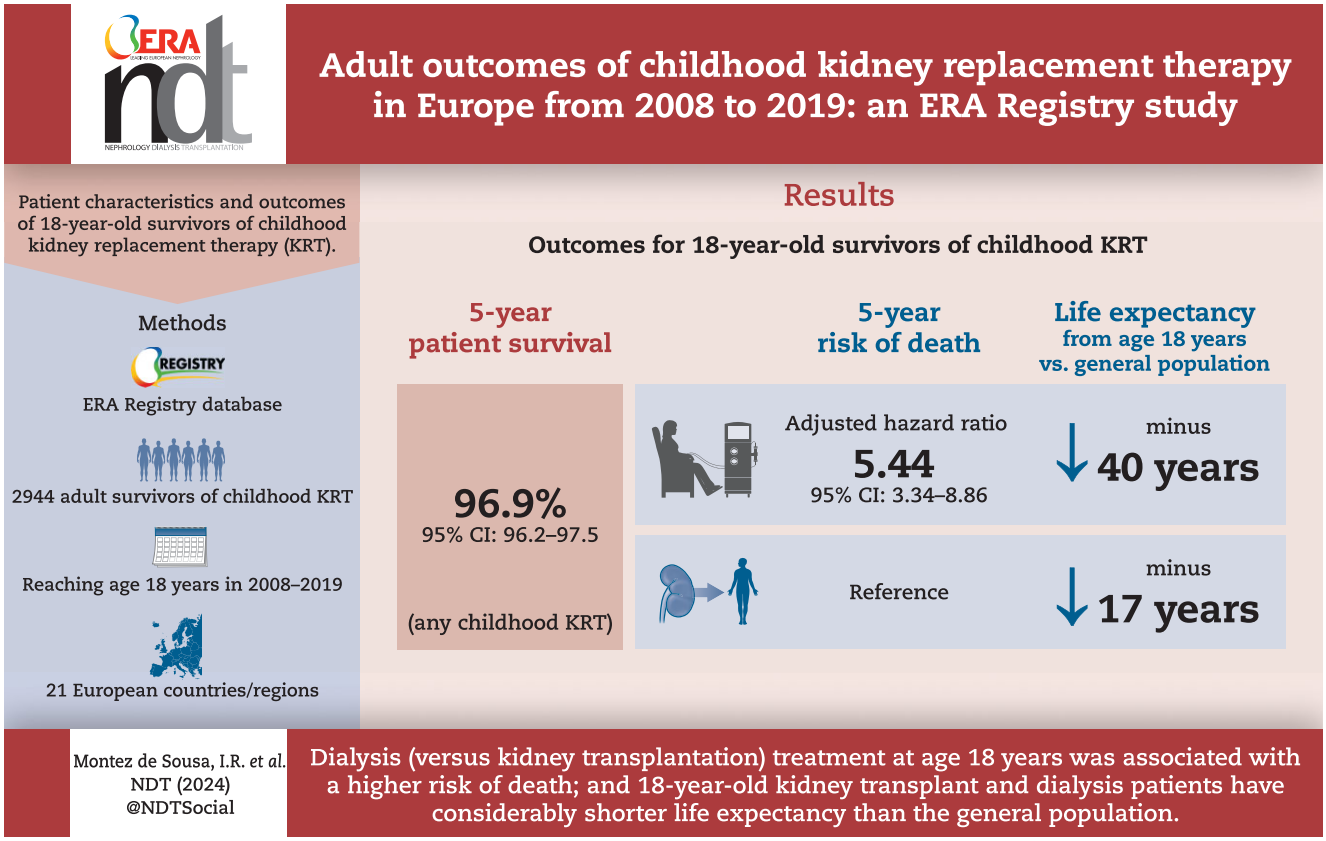
**Methods.** Data on KRT patients reaching their 18th birthday in 2008–19 were collected from 21 European countries/regions providing individual patient data to the European Renal Association (ERA) Registry. Patient characteristics and treatment trajectories were examined before and after turning 18 years old. Kaplan–Meier and Cox proportional hazards regression were used for patient and graft survival analyses.

**Results.** In total, 2944 patients were included. The proportion of adult survivors initiating KRT at a very young age (0–4 years) and undergoing pre-emptive kidney transplantation increased. Unadjusted 5-year patient survival was 96.9% [95% confidence interval (CI) 96.2–97.5]. Dialysis patients had a higher risk of death than kidney transplant recipients [adjusted hazard ratio 5.44 (95% CI 3.34–8.86)]. Between ages 18 and 23 years, about 21% of the adult survivors lost their kidney transplant and 34% of the dialysis patients continued this treatment. Compared with the general population, life expectancy for 18-year-old kidney transplant and dialysis patients was 17 and 40 years shorter, respectively.

**Conclusion.** Life expectancy of 18-year-old kidney transplant recipients was lower compared with the general population, yet having a functioning kidney graft at age 18 years resulted in better outcomes than being on dialysis. Nevertheless, between ages 18 and 23 years, about one-fifth of the kidney grafts failed and one-third of the patients remained on dialysis.

**Keywords:** kidney replacement therapy, kidney transplantation, paediatric nephrology, transition, young adults

## GRAPHICAL ABSTRACT




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## KEY LEARNING POINTS

**What was known:**

- Adolescents and young adults on kidney replacement therapy (KRT) are a 'high-risk' population, going through a sensitive transition period from paediatric to adult nephrology centres; at this point they are expected to take responsibility for their own treatment, which is believed to contribute to an increased risk of kidney graft failure.
- In a previous European Renal Association Registry study, an increase in the rate (per million age-related population, Pmarp) of 18-year-old survivors of childhood KRT between 1985 and 2004 was reported; within this period, patient survival was good, with an unadjusted 5-year survival rate of 95.1% (95% confidence interval 93.9–96.0).
- No recent European data exist for this challenging population.

**This study adds:**

- The rate (Pmarp) of adult survivors of childhood KRT reaching their 18th birthday remained stable between 2008 and 2019, yet there was a tendency to initiate KRT at a younger age and with a pre-emptive kidney transplant.
- Being treated with dialysis vs kidney transplantation at age 18 years and a longer dialysis vintage during childhood were associated with a higher risk of death; about 21% of the kidney grafts failed between ages 18 and 23 years.
- Life expectancy for 18-year-old kidney transplant and dialysis patients was 17 and 40 years shorter, respectively, compared with the general population; besides, among 18-year-old dialysis patients, females had a shorter life expectancy than males.

**Potential impact:**

- This study can support healthcare providers, policy makers, patients and their families by providing information on the prognosis of adult survivors of childhood KRT, and where applicable, in recognizing opportunities to improve care in this specific patient group undergoing the challenging period of transitioning from paediatric to adult nephrology care.
- Life expectancy of KRT patients at age 18 years is already shorter compared with healthy peers, especially for dialysis patients and for females; potential strategies to decrease the time on dialysis and to reduce sex disparities in adult survivors of childhood KRT should be explored.

## INTRODUCTION

Young adults with childhood kidney failure, undergoing kidney replacement therapy (KRT), represent a challenging patient group. Besides experiencing major life changes associated with adolescence, transition from paediatric to adult nephrology care requires patients to take responsibility for their own treatment. This is believed to contribute to poor treatment adherence, leading to a high kidney graft failure risk [1–3].

Despite challenges faced by these patients entering adult renal centres, few studies have focused on the epidemiology of KRT during adolescence and young adulthood [2, 4]. Available data either concern single countries [4, 5] or are outdated [2]. Studies on the transition from paediatric to adult nephrology care exploring the outcomes in adulthood of survivors of childhood KRT would support healthcare providers, patients and their families, and policy makers by providing knowledge about the prognosis of this high-risk population and recognizing opportunities for improved patient care [4, 6, 7].

Fifteen years ago, Kramer *et al.* reported the characteristics, treatment history and survival of patients who initiated KRT during childhood and reached age 18 years (i.e. adult survivors of childhood KRT) between 1985 and 2004 in Europe [2]. Since then, the number of patients starting KRT during childhood and their survival have increased, resulting in a higher expected number of KRT patients reaching adulthood and transferring to adult nephrology centres [8]. Furthermore, the paediatric KRT population has changed as younger patients and more patients with comorbidities are now accepted into KRT programmes [8–10].

The aim of this study was to provide an update on patient characteristics, treatment history, patient and kidney graft survival, and expected remaining lifetime of adult survivors of childhood KRT in Europe, between 2008 and 2019. In addition, we aimed to report the 5-year prognosis (at age 23 years) of adult survivors of childhood KRT.

## MATERIALS AND METHODS

### Patient population and data sources

Individual patient data was extracted from the European Renal Association (ERA) Registry, which collects data on KRT patients from national/regional renal registries in Europe, including month/year of birth, sex, primary renal disease (PRD), date and modality of first KRT, KRT modality changes and date and cause of death [11].

Patients included in this study started KRT during childhood and turned 18 years in 2008–19, i.e. adult survivors of childhood KRT; Fig. 1 contains a detailed explanation of this patient group. These patients originated from the following countries: Austria, Denmark, Finland, Greece, Iceland, Spain (contributing regions are shown in Supplementary data, Table S1), the Netherlands, Norway, Sweden, and the UK. Almost all participating countries/regions had full coverage of their general population.

To calculate the contribution of adult survivors of childhood KRT to the total number of patients starting KRT in 'adult' centres in 2008–19, the number of incident adult patients (≥18 years) from the included countries was obtained from the ERA Registry [11]. Expected remaining lifetime at age 18 years was calculated using ERA Registry data from all KRT patients from the abovementioned countries. General population data and expected remaining lifetimes at age 18 years were extracted from the Eurostat database (for the countries/regions included in this study reflecting the same period) [12, 13].

### Statistical analyses

Data are presented as number and percentage, median and interquartile range (IQR) and per million age-related population (Pmarp), as appropriate. Chi-square tests were performed to assess statistical differences in categorical variables.

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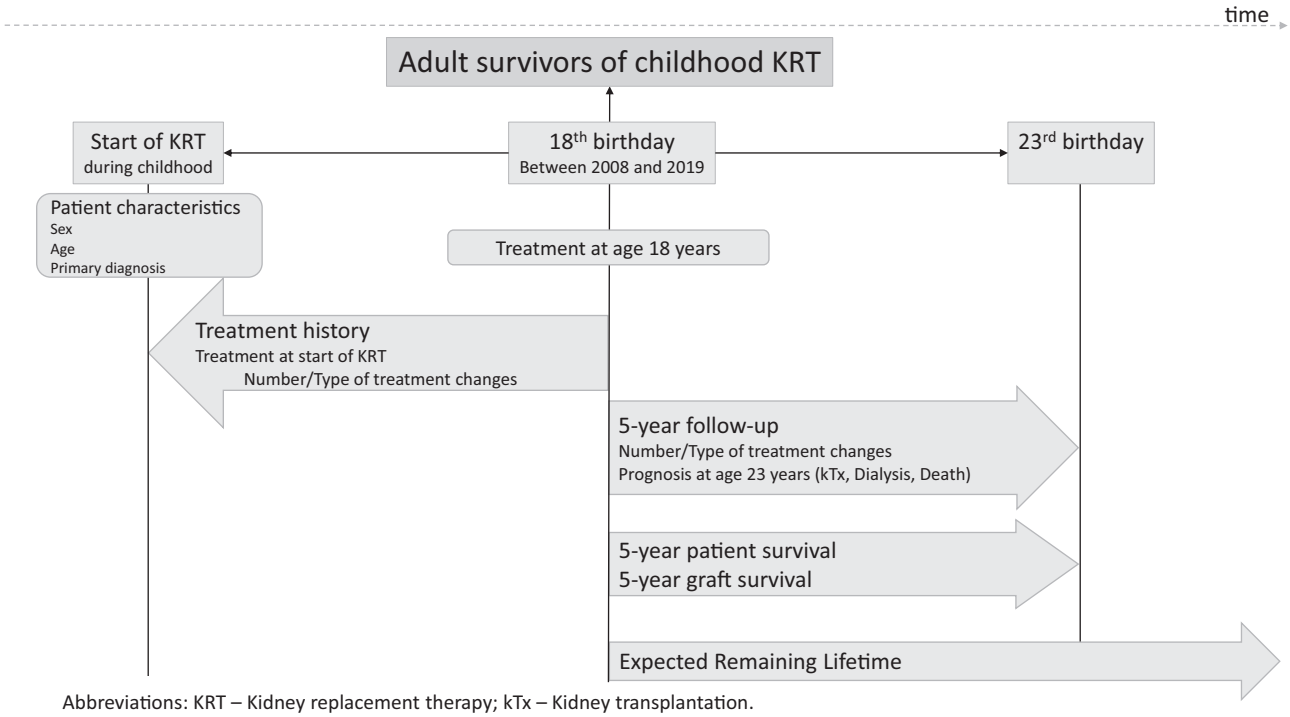
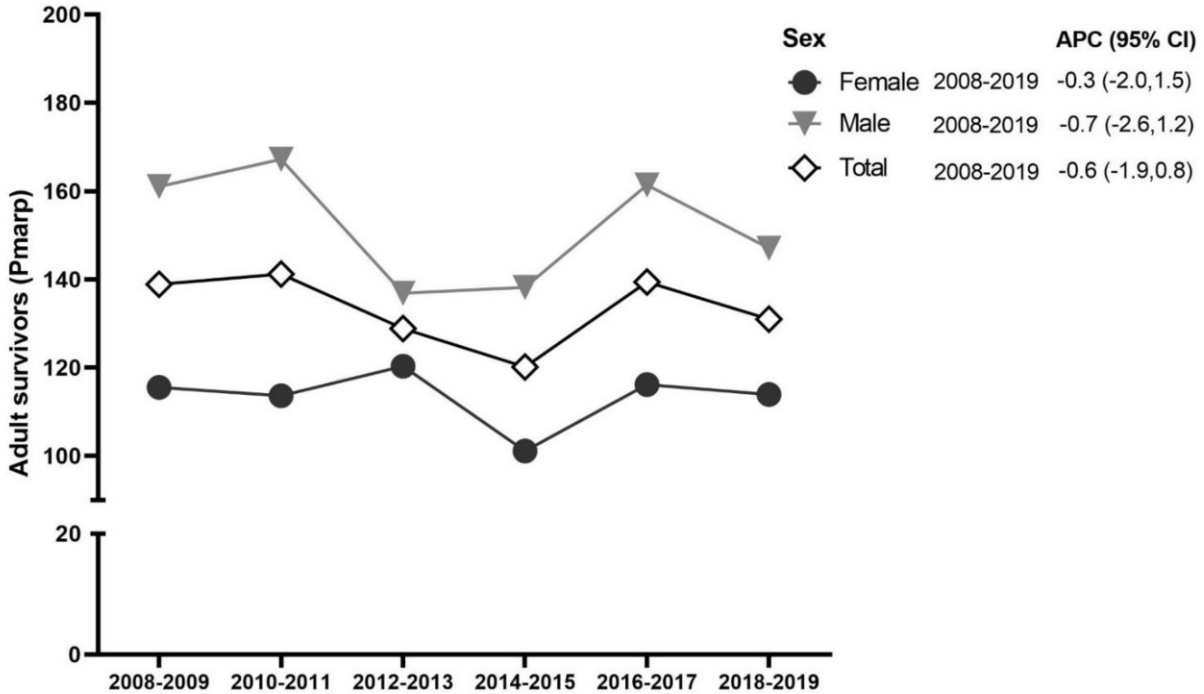



**Figure 1:** Flowchart illustrating adult survivors of childhood KRT and associated variables and analyses.




| | 2008-2009 | 2010-2011 | 2012-2013 | 2014-2015 | 2016-2017 | 2018-2019 |
|---|---|---|---|---|---|---|
| **Female (Pmarp)** | 115.5 | 113.6 | 120.3 | 101.1 | 116.1 | 113.9 |
| **Male (Pmarp)** | 161.1 | 167.2 | 136.9 | 138.2 | 161.4 | 147.1 |
| **Total (Pmarp)** | 138.9 | 141.2 | 128.8 | 120.1 | 139.4 | 131.0 |

Abbreviations: Pmarp - Per million age-related population; APC - Annual percentage change

**Figure 2:** Trends in the rate (Pmarp) of KRT patients reaching age 18 years, overall, and stratified by sex (between 2008 and 2019).

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**Table 1:** Characteristics of adult survivors of childhood KRT, overall and by period in which age 18 years was reached.

| | | Period in which age 18 years was reached | | | |
|---|---|---|---|---|---|
| | **All patients N (%)** | **2008–11 N (%)** | **2012–15 N (%)** | **2016–19 N (%)** | **P-value[a]** |
| All | 2944 | 1060 | 910 | 974 | |
| Age at start of KRT, years | | | | | |
| 0–4 | 522 (17.7) | 166 (15.7) | 156 (17.1) | 200 (20.5) | .016 |
| 5–9 | 551 (18.7) | 210 (19.8) | 165 (18.1) | 176 (18.1) | |
| 10–14 | 969 (32.9) | 356 (33.6) | 326 (35.8) | 287 (29.5) | |
| 15–17 | 902 (30.6) | 328 (30.9) | 263 (28.9) | 311 (31.9) | |
| Sex | | | | | |
| Male | 1726 (58.6) | 638 (60.2) | 516 (56.7) | 572 (58.7) | .293 |
| PRD | | | | | |
| CAKUT | 1141 (38.8) | 417 (39.3) | 330 (36.3) | 394 (40.5) | .203 |
| Glomerulonephritis | 487 (16.5) | 185 (17.5) | 157 (17.3) | 145 (14.9) | |
| Cystic kidney disease | 271 (9.2) | 98 (9.2) | 86 (9.5) | 87 (8.9) | |
| Hereditary nephropathy | 235 (8.0) | 75 (7.1) | 74 (8.1) | 86 (8.8) | |
| Ischaemic renal failure | 46 (1.6) | 11 (1.0) | 14 (1.5) | 21 (2.2) | |
| HUS | 81 (2.8) | 27 (2.5) | 31 (3.4) | 23 (2.4) | |
| Metabolic disorders | 87 (3.0) | 37 (3.5) | 28 (3.1) | 22 (2.3) | |
| Vasculitis | 64 (2.2) | 17 (1.6) | 26 (2.9) | 21 (2.2) | |
| Miscellaneous | 185 (6.3) | 65 (6.1) | 66 (7.3) | 54 (5.5) | |
| Unknown | 347 (11.8) | 128 (12.1) | 98 (10.8) | 121 (12.4) | |
| Treatment at start of KRT | | | | | |
| Haemodialysis | 948 (32.2) | 339 (32.0) | 283 (31.1) | 326 (33.5) | .002 |
| Peritoneal dialysis | 1112 (37.8) | 436 (41.1) | 360 (39.6) | 316 (32.4) | |
| Unknown | 42 (1.4) | 14 (1.3) | 12 (1.3) | 16 (1.6) | |
| Kidney transplantation | 842 (28.6) | 271 (25.6) | 255 (28.0) | 316 (32.4) | |
| Deceased donor graft | 316 (37.5) | 109 (40.2) | 92 (36.1) | 115 (36.4) | |
| Living donor graft | 510 (60.6) | 151 (55.7) | 160 (62.7) | 199 (63.0) | |
| Unknown donor type | 16 (1.9) | 11 (4.1) | 3 (1.2) | 2 (0.6) | |

[a]P-values resulting from chi-square tests comparing periods in which age 18 years was reached.
HUS, haemolytic uremic syndrome.

The number of patients reaching age 18 years (Pmarp) was calculated, overall and by sex, dividing the number of KRT patients turning 18 years old per calendar year by the number of young adults in the general population reaching this age. Time trends were studied using Joinpoint regression. This method estimates the annual percentage change, the linear slope of a trend computed with Poisson regression [14].

Patient characteristics and treatment history were stratified by period of turning 18 years (2008–11, 2012–15 or 2016–19). PRDs were grouped according to ERA Registry codes adapted for children, detailed information on the diseases included in each PRD group are described elsewhere [11]. For comparison reasons, PRD categories were also grouped as in the aforementioned paper from Kramer *et al.* [2].

A 5-year follow-up analysis was performed from the patients' 18th birthday onwards, exploring treatment trajectories between ages 18 and 23 years. Only patients who turned 18 years in 2008–15 (2008–14 in Scotland) were included in these analyses, because younger patients could not reach the 5-year follow-up within the study period. Follow-up ended on 31 December 2019 for patients from Scotland and 31 December 2020 for other countries.

Kaplan–Meier and Cox regression analyses were used to determine 5-year patient and graft survival, and risk factors for mortality and graft failure. For patient survival, patients were followed from their 18th birthday until death, or censored in case of recovery of kidney function, loss to follow-up or end of the study period, whichever occurred first, adjusted for potential confounders [15]. For kidney graft survival, follow-up commenced on patients' 18th birthday until graft failure (i.e. death or returning to dialysis) and was censored in case of loss to follow-up or end of the study period. All models were adjusted for potential confounders when appropriate, i.e. sex, PRD, country, age at KRT onset, age at kidney transplantation and donor type [15]. Additional graft survival analyses were performed for patients 5 years younger and older (13 and 23 years) than 18 years.

The expected remaining lifetime of KRT patients at age 18 years was calculated overall, by sex and stratified by treatment modality at 18 years. Although the true expected remaining lifetime remains unknown until all patients in the group have died, it can be projected assuming patients will die at the same rates as observed in older groups. Hence, to project the expected remaining lifetime of 18 year olds on KRT, we used mortality data on older prevalent KRT patients [11]. These results were compared with weighted averages of the expected remaining lifetime of the general population [11], calculated based on the total population aged 18 years in each country.

As various countries were included in this study, potential differences could be a concern when interpreting the results, however a previous European Society for Paediatric Nephrology (ESPN)/ERA Registry study found similar kidney transplantation rates and graft survival within high-income countries [16]. From the countries included, only Greece had a lower GDP [17]. Sensitivity analyses excluding Greece were performed (data not shown), the results were similar to the overall analyses.

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**Table 2:** Treatment history of adult survivors of childhood KRT, overall and by period in which age 18 years was reached.

| | All patients N (%) | Period in which age 18 years was reached | | | P-value[a] |
|---|---|---|---|---|---|
| | | 2008–11 N (%) | 2012–15 N (%) | 2016–19 N (%) | |
| Years spent on KRT before age 18 years [median (IQR)] | 5.5 (2.4–10.6) | 5.4 (2.3–10.3) | 5.5 (2.6–10.5) | 5.5 (2.1–11.5) | |
| Treatment modality at age 18 years | | | | | |
| Haemodialysis | 358 (12.2) | 137 (12.9) | 111 (12.2) | 110 (11.3) | .310 |
| Peritoneal dialysis | 149 (5.1) | 61 (5.8) | 44 (4.8) | 44 (4.5) | |
| Unknown | 40 (1.4) | 12 (1.1) | 18 (2.0) | 10 (1.0) | |
| Kidney transplantation | 2397 (81.4) | 850 (80.2) | 737 (81.0) | 810 (83.2) | |
| Deceased donor graft | 1340 (45.5) | 494 (46.6) | 423 (46.5) | 423 (43.4) | |
| Living donor graft | 989 (33.6) | 322 (30.4) | 299 (32.9) | 368 (37.8) | |
| Unknown donor type | 68 (2.3) | 34 (3.2) | 15 (1.6) | 19 (2.0) | |
| Number of treatment changes between the start of KRT and age 18 years | | | | | |
| 0 | 1094 (37.2) | 376 (35.5) | 319 (35.1) | 399 (41.0) | .011 |
| 1 | 1233 (41.9) | 466 (44.0) | 380 (41.8) | 387 (39.7) | |
| 2 | 341 (11.6) | 107 (10.1) | 122 (13.4) | 112 (11.5) | |
| ≥3 | 276 (9.4) | 111 (10.5) | 89 (9.8) | 76 (7.8) | |
| Type of treatment changes between the start of KRT and age 18 years[b] | | | | | |
| HD→PD | 275 (6.9) | 85 (5.9) | 95 (7.5) | 95 (7.3) | <.001 |
| HD→kTx | 906 (22.6) | 317 (21.9) | 286 (22.7) | 303 (23.3) | |
| PD→HD | 342 (8.5) | 112 (7.7) | 122 (9.7) | 108 (8.3) | |
| PD→kTx | 1015 (25.3) | 408 (28.2) | 319 (25.3) | 288 (22.2) | |
| kTx→HD | 255 (6.4) | 89 (6.2) | 88 (7.0) | 78 (6.0) | |
| kTx→PD | 117 (2.9) | 60 (4.1) | 30 (2.4) | 27 (2.1) | |
| None | 1094 (27.3) | 376 (26.0) | 319 (25.3) | 399 (30.7) | |

[a]P-values resulting from chi-square tests comparing periods in which age 18 years was reached.
[b]Patients may occur in more than one category.
HD, haemodialysis; PD, peritoneal dialysis; kTx, kidney transplantation.

Statistical tests were two-tailed and differences were considered statistically significant with *P*-values <.05. Data analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

In 2008–19, 3090 patients who started KRT during childhood turned 18 years of age. This added 1.2% to the total number of adults (≥18 years; $n = 250\,462$) initiating KRT in the same period and countries. Of these, 146 patients had an unknown date of KRT onset and were excluded from further analyses. A total of 2944 patients were included in the study.

Between 2008 and 2019, the rate of adult survivors of childhood KRT remained stable around 133 Pmarp, with consistently more males than females (Fig. 2).

### Patient characteristics

Most patients initiated KRT between 10–14 (32.9%) and 15–17 (30.6%) years of age (Table 1). However, the proportion of adult survivors of childhood KRT initiating treatment at very young age (0–4 years) increased from 15.7% in 2008–11 to 20.5% in 2016–19.

The most common PRDs were congenital anomalies of the kidney and urinary tract (CAKUT) (38.8%) and glomerulonephritis (16.5%), whereas 11.8% of patients had unknown/missing PRDs (Table 1). Following the categorization from Kramer *et al.*, hypoplasia/dysplasia (20.8%) and pyelonephritis (17.9%) were most common (Supplementary data, Table S2).

Most adult survivors received peritoneal dialysis (37.8%) or haemodialysis (32.2%) as the initial treatment modality. Nevertheless, the proportion of patients initiating KRT with pre-emptive kidney transplantation increased from 25.6% for patients turning 18 years in 2008–11 to 32.4% in 2016–19 (Table 1).

### Treatment history

Adult survivors of childhood KRT spent a median of 5.5 (IQR 2.4–10.6) years on KRT before their 18th birthday, the majority (81.4%) reached this age with a functioning kidney graft (45.5% from deceased donors, 33.6% from living donors and for 2.3% donor type was unknown) (Table 2). Subgroup analysis showed that the younger adult survivors were at time of KRT onset, the more likely they were to have a functioning kidney transplant by their 18th birthday (Supplementary data, Table S3). For most adult survivors of childhood KRT, the treatment modality either remained the same from KRT onset until their 18th birthday (37.2%) or they experienced one modality change (41.9%). Most treatment changes were from haemodialysis or peritoneal dialysis to kidney transplantation (22.6% and 25.3%, respectively). Between 2008 and 2019, the number of treatment changes decreased ($P = .011$) (Table 2).

Overall, 12.8% of patients did not receive a kidney transplant from KRT onset until their 18th birthday [median dialysis vintage before 18th birthday: 1.9 (IQR 1.0–3.6) years], while 80.5% received one, 6.1% received two and 0.6% received three or more kidney transplants (Supplementary data, Table S3).

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**Table 3:** Prognosis of adult survivors of childhood KRT during the first 5 years after reaching age 18 years, by age at KRT onset.

| | | Age at KRT onset | | | | |
|---|---|---|---|---|---|---|
| | **All patients N (%)** | **0–4 N (%)** | **5–9 N (%)** | **10–14 N (%)** | **15–17 N (%)** | **P-value[a]** |
| All[b] | 1854 | 313 | 351 | 640 | 550 | |
| Number of deaths | 65 (3.5) | 9 (2.9) | 10 (2.8) | 20 (3.1) | 26 (4.7) | .319 |
| Mortality rate[c] | 7.2 | 5.8 | 5.8 | 6.4 | 9.7 | |
| Causes of death | | | | | | |
| Cardiovascular disease | 11 (16.9) | 0 (0.0) | 3 (30.0) | 1 (5.0) | 7 (26.9) | N/A[d] |
| Infection | 11 (16.9) | 1 (11.1) | 1 (10.0) | 3 (15.0) | 6 (23.1) | |
| Malignancy | 7 (10.8) | 2 (22.2) | 2 (20.0) | 1 (5.0) | 2 (7.7) | |
| Other | 20 (30.8) | 2 (22.2) | 2 (20.0) | 7 (35.0) | 9 (34.6) | |
| Missing | 16 (24.6) | 4 (44.4) | 2 (20.0) | 8 (40.0) | 2 (7.7) | |
| Treatment modality at age 23 years (for those alive) | | | | | | |
| Haemodialysis | 293 (16.4) | 54 (17.8) | 50 (14.7) | 102 (16.5) | 86 (16.6) | .607 |
| Peritoneal dialysis | 37 (2.1) | 5 (1.6) | 6 (1.8) | 18 (2.9) | 8 (1.5) | |
| Kidney transplantation | 1459 (81.6) | 245 (80.6) | 285 (83.6) | 500 (80.6) | 429 (81.9) | |
| Deceased donor graft | 785 (43.9) | 145 (47.7) | 165 (48.4) | 255 (41.1) | 220 (42.0) | |
| Living donor graft | 611 (34.2) | 82 (27.0) | 104 (30.5) | 230 (37.1) | 195 (37.2) | |
| Unknown donor type | 63 (3.5) | 18 (5.9) | 16 (4.7) | 15 (2.4) | 14 (2.7) | |
| Number of treatment changes between age 18 and 23 years | | | | | | |
| 0 | 1314 (70.9) | 229 (73.2) | 268 (76.4) | 492 (76.9) | 325 (59.1) | <.001 |
| 1 | 349 (18.8) | 50 (16.0) | 51 (14.5) | 95 (14.8) | 153 (27.8) | |
| 2 | 144 (7.8) | 26 (8.3) | 25 (7.1) | 32 (5.0) | 61 (11.1) | |
| ≥3 | 47 (2.5) | 8 (2.6) | 7 (2.0) | 21 (3.3) | 11 (2.0) | |
| Type of treatment changes between age 18 and 23 years[e] | | | | | | |
| HD→PD | 49 (2.3) | 6 (1.7) | 3 (0.8) | 22 (3.0) | 18 (2.8) | <.001 |
| HD→kTx | 221 (10.5) | 30 (8.4) | 30 (7.7) | 45 (6.2) | 116 (18.1) | |
| PD→HD | 107 (5.1) | 13 (3.6) | 12 (3.1) | 40 (5.5) | 42 (6.5) | |
| PD→kTx | 80 (3.8) | 6 (1.7) | 9 (2.3) | 10 (1.4) | 55 (8.6) | |
| kTx→HD | 267 (12.6) | 59 (16.5) | 52 (13.3) | 90 (12.4) | 66 (10.3) | |
| kTx→PD | 76 (3.6) | 14 (3.9) | 17 (4.3) | 25 (3.5) | 20 (3.1) | |
| None | 1314 (62.2) | 229 (64.1) | 268 (68.5) | 492 (68.0) | 325 (50.6) | |

[a]P-values resulting from chi-square tests comparing age groups at KRT onset.
[b]Only the 1854 adult survivors of childhood KRT who could reach a follow-up of 5 years within the study period were included in these analyses.
[c]Per 1000 person-years.
[d]A P-value was not calculated for causes of death because the frequency was too low.
[e]Patients may occur in more than one category.
HD, haemodialysis; PD, peritoneal dialysis; kTx, kidney transplantation

## Five-year prognosis

Only adult survivors of childhood KRT who reached their 23rd birthday before the end of study period were included in this analysis ($n$ = 1854, 63%) (Table 3). Similar patient characteristics were observed to those of the total group ($n$ = 2944; Supplementary data, Table S4).

The percentage of patients who reached their 23rd birthday with a functioning kidney transplant (81.6%; Table 3) was similar to that of patients with a functioning graft at age 18 years (81.4%). Adult survivors who initiated KRT at age 15–17 years experienced most treatment changes in the 5 years after their 18th birthday ($P$ < .001), mainly from haemodialysis to kidney transplantation (18.1%) (Table 3). Of the adult survivors of childhood KRT with a functioning kidney transplant at their 18th birthday ($n$ = 1526), 14% switched to dialysis prior to their 23rd birthday and 2% died. Among patients on dialysis at age 18 years ($n$ = 328), 55% received a kidney transplant, 34% remained on dialysis and 10% died within 5 years (Fig. 3).

## Patient survival

From their 18th birthday onwards, the unadjusted 5-year patient survival was 96.9% [95% confidence interval (CI) 96.2–97.5]. Treatment modality at age 18 years and cumulative time spent on dialysis before 18th birthday were significantly associated with mortality risk (Table 4). Adult survivors of childhood KRT receiving dialysis at age 18 years showed a more than five times higher risk of death compared with those with a kidney transplant [adjusted hazard ratio (aHR) 5.44 (95% CI 3.34–8.86)].

## Graft survival

For adult survivors of childhood KRT with a kidney transplant at age 18 years, median time spent with the functioning graft before their 18th birthday was 4.9 (IQR 2.1–9.4) years, with a significant sex difference [4.5 (IQR 2.0–8.6) years for females and 5.0 (IQR 2.1–9.9) years for males; $P$ = .030].

After their 18th birthday, the unadjusted 5-year graft survival was 78.9% (95% CI 77.1–80.7; Table 5). For those experiencing graft failure, median kidney graft failure age was 21.3 (IQR 19.6–23.7) years. For comparison, 5-year graft survival rates of patients 5 years younger (13 years) and older (23 years) were calculated [88.4% (95% CI 86.5–90.2) and 81.9% (95% CI 80.5–83.3), respectively]. Eighteen-year-old patients had a significantly higher risk of graft failure than 13 and 23 year olds (Supplementary data, Table S5).

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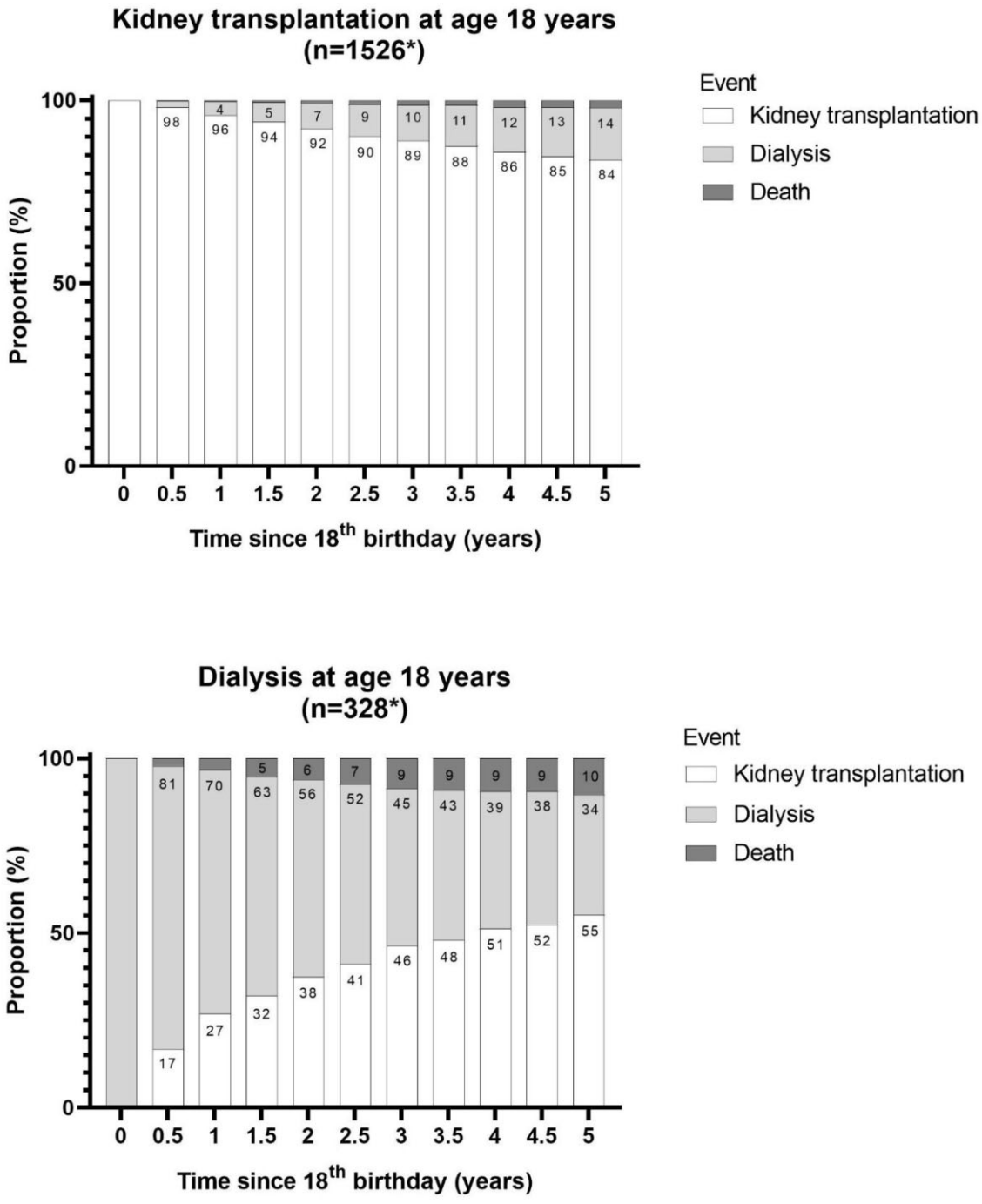



**Figure 3:** Prognosis of adult survivors of childhood KRT during the first 5 years after reaching age 18 years, by treatment modality at age 18 years.

## Expected remaining lifetime

In 2008–19, the average expected remaining lifetime of 18 year olds with a functioning kidney graft was 47.4 years (74% of that of the general population; loss of 16.6 years), for 18 year olds on dialysis, the average expected remaining lifetime was 23.8 years (37% of that of the general population; loss of 40.3 years) (Fig. 4).

Females on KRT showed a greater loss of expected remaining years of life than males, particularly when on dialysis at age 18 years [loss of 66% (43.6 years) in females and 60% (37.1 years) in males].

Overall, the expected remaining lifetime of 18-year-old KRT patients with a functioning kidney transplant increased over time (Fig. 4). For 18-year-old dialysis patients, males seemed to show

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**Table 4:** Five-year survival probabilities and hazard ratios for mortality of adult survivors of childhood KRT (from age 18 years onwards) unadjusted and after adjustment for potential confounders.

| | | | | HR (95% CI) for death | |
|---|---|---|---|---|---|
| | $N_{start}$ | $N_{death}$ | 5-year survival (95% CI) | Unadjusted | Adjusted |
| All | 2944 | 80 | 96.9 (96.2–97.5) | | |
| Age at KRT onset, years[e] | | | | | |
| 0–4 | 522 | 11 | 97.4 (95.6–98.7) | 0.56 (0.28–1.10) | 0.60 (0.30–1.23) |
| 5–9 | 551 | 11 | 97.7 (96.2–98.9) | 0.51 (0.26–1.01) | 0.57 (0.28–1.14) |
| 10–14 | 969 | 24 | 97.3 (96.1–98.3) | 0.63 (0.38–1.07) | 0.68 (0.40–1.16) |
| 15–17 | 902 | 34 | 95.5 (93.9–96.9) | 1 (ref) | 1 (ref) |
| Sex | | | | | |
| Female | 1218 | 39 | 96.3 (95.1–97.4) | 1 (ref) | |
| Male | 1726 | 41 | 97.3 (96.4–98.0) | 0.74 (0.48–1.14) | |
| PRD[f] | | | | | |
| CAKUT | 1141 | 22 | 97.7 (96.6–98.6) | 1 (ref) | 1 (ref) |
| Glomerulonephritis | 487 | 15 | 96.7 (94.8–98.1) | 1.59 (0.82–3.06) | 1.52 (0.78–2.95) |
| Cystic kidney disease | 271 | 6 | 97.5 (95.1–99.1) | 1.13 (0.46–2.79) | 1.08 (0.44–2.69) |
| Hereditary nephropathy | 235 | 8 | 96.0 (92.9–98.3) | 1.81 (0.81–4.07) | 1.75 (0.77–3.94) |
| Ischaemic renal failure | 46 | 0 | 100.0 (100.0-.) | [d] | [d] |
| HUS | 81 | 3 | 95.4 (88.9–99.1) | 1.89 (0.57–6.33) | 1.78 (0.53–5.99) |
| Metabolic disorders | 87 | 2 | 97.5 (93.0–99.8) | 1.17 (0.27–4.96) | 1.14 (0.27–4.88) |
| Vasculitis | 64 | 1 | 97.7 (91.1–100.0) | 0.83 (0.11–6.13) | 0.78 (0.10–5.72) |
| Miscellaneous | 185 | 7 | 95.9 (92.3–98.3) | 1.94 (0.83–4.55) | 1.88 (0.80–4.43) |
| Unknown | 347 | 16 | 94.6 (91.7–96.9) | **2.49 (1.31–4.73)** | **2.37 (1.23–4.55)** |
| Treatment at age 18 years[a,b,g] | | | | | |
| Dialysis | 507 | 41 | 90.9 (88.1–93.4) | **5.34 (3.43–8.30)** | **5.44 (3.34–8.86)** |
| Haemodialysis | 358 | 33 | 89.5 (85.9–92.7) | **6.16 (3.86–9.82)** | **6.15 (3.71–10.21)** |
| Peritoneal dialysis | 149 | 8 | 94.2 (89.6–97.5) | **3.44 (1.61–7.38)** | **3.53 (1.57–7.91)** |
| Kidney transplantation | 2397 | 38 | 98.1 (97.5–98.7) | 1 (ref) | 1 (ref) |
| Cumulative time spent on dialysis between KRT onset and age 18 years[c,g] | | | | | |
| 0 years | 770 | 9 | 98.5 (97.4–99.3) | 1 (ref) | 1 (ref) |
| >0–1 years | 849 | 18 | 97.5 (96.2–98.5) | 1.81 (0.81–4.04) | 1.70 (0.75–3.82) |
| >1–3 years | 830 | 27 | 96.5 (95.0–97.7) | **2.79 (1.31–5.93)** | **2.73 (1.26–5.90)** |
| >3 years | 428 | 25 | 93.5 (90.8–95.8) | **4.87 (2.28–10.44)** | **5.57 (2.53–12.25)** |

[a]Two separate models are presented, one for the analysis with dialysis as an overall class and another with haemodialysis and peritoneal dialysis as separate classes.
[b]Forty participants had unknown treatment modality at age 18 years.
[c]Sixty-seven patients had unknown treatment modality at KRT onset and/or at age 18 years, hence their total time on dialysis could not be calculated.
[d]The number of events was too low to obtain an effect estimate.
[e]Adjusted for sex, PRD and country.
[f]Adjusted for sex and country.
[g]Adjusted for sex, PRD, age at KRT onset and country.
HUS, haemolytic uremic syndrome.
Bold values represent factors that were statistically significantly associated with mortality.

slight improvement over the study period; no improvement was observed for females.

## DISCUSSION

This study focussed on adult survivors of childhood KRT, a unique and overlooked patient group going through a sensitive transition period from paediatric to adult nephrology care with high impact on health outcomes. We provided an update on their characteristics, treatment history and prognosis over the last decade (2008–19). There was an increase in the proportion of adult survivors initiating KRT at very young age and with pre-emptive kidney transplantation. Among patients who reached their 18th birthday with a functioning kidney transplant, about one-fifth lost their graft before age 23 years, and one-third of patients on dialysis at age 18 years remained on dialysis until they turned 23 years of age. Eighteen-year-old females on KRT, particularly when on dialysis, had shorter expected remaining lifetimes than males, suggesting that the survival advantage of females was lost [18].

### Changes in patient characteristics and treatment history

Compared with the findings of Kramer *et al.* [2], the number of adult survivors of childhood KRT reaching age 18 years increased from 71 Pmarp in 1985 to 116 Pmarp in 2004 and to 143 Pmarp in 2008, but remained stable afterwards (141 Pmarp in 2019) (Supplementary data, Fig. S1). Thus the number of patients transferring from paediatric to adult nephrology care has also increased. This might be explained by a higher number of paediatric patients starting KRT and their improved survival in the late 1990s and early 2000s [2, 19]. Adult survivors of childhood KRT tended to initiate treatment at younger age, spending more time on KRT before reaching adulthood. Simultaneously, more adult survivors were diagnosed with CAKUT [2]. CAKUT is among the leading causes of kidney failure in children, often diagnosed at a very young age [11]. This diagnosis has been associated with better graft survival and may therefore be one of the reasons for a higher likelihood of having a functioning kidney graft at age 18 years when initiating KRT at younger age [20]. Furthermore, the shift

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**Table 5:** Five-year kidney graft survival probabilities and hazard ratios for graft failure of adult survivors of childhood KRT (from age 18 years onwards), unadjusted and after adjustment for potential confounders.

| | | | | HR (95% CI) for graft failure | |
|---|---|---|---|---|---|
| | $N_{start}$ | $N_{failure}$ | 5-year survival (95% CI) | Unadjusted | Adjusted |
| All | 2397 | 426 | 78.9 (77.1–80.7) | | |
| Age at kidney transplantation (for grafts functioning at age 18 years)[a,c], years | | | | | |
| 0–4 | 301 | 56 | 76.3 (70.65–81.7) | 1.12 (0.82–1.53) | 1.10 (0.80–1.52) |
| 5–9 | 440 | 71 | 80.6 (76.3–84.6) | 0.92 (0.69–1.22) | 0.93 (0.70–1.25) |
| 10–14 | 819 | 156 | 78.1 (75.0–81.1) | 1.07 (0.85–1.34) | 1.08 (0.86–1.36) |
| 15–17 | 822 | 143 | 79.3 (76.1–82.3) | 1 (ref) | 1 (ref) |
| Sex | | | | | |
| Female | 977 | 187 | 77.2 (74.2–80.1) | 1 (ref) | |
| Male | 1420 | 239 | 80.0 (77.7–82.3) | 0.87 (0.72–1.05) | |
| Type of kidney transplant[b,d] | | | | | |
| Living donor graft | 989 | 157 | 81.0 (78.2–83.6) | 1 (ref) | 1 (ref)[a] |
| Deceased donor graft | 1340 | 256 | 77.4 (74.8–79.8) | **1.20 (1.02–1.42)** | **1.24 (1.01–1.51)**[a] |
| PRD[e] | | | | | |
| CAKUT | 1000 | 189 | 77.6 (74.6–80.4) | 1 (ref) | 1 (ref) |
| Glomerulonephritis | 352 | 67 | 78.3 (73.4–82.7) | 1.01 (0.77–1.34) | 0.98 (0.74–1.30) |
| Cystic kidney disease | 243 | 42 | 80.1 (74.4–85.3) | 0.90 (0.65–1.26) | 0.87 (0.62–1.22) |
| Hereditary nephropathy | 192 | 37 | 74.9 (67.4–81.7) | 1.03 (0.73–1.47) | 1.02 (0.72–1.45) |
| Ischaemic renal failure | 37 | 1 | 95.8 (84.4–100.0) | 0.14 (0.02–1.00) | **0.14 (0.02–0.97)** |
| HUS | 68 | 12 | 80.4 (69.5–89.4) | 0.93 (0.52–1.67) | 0.88 (0.50–1.59) |
| Metabolic disorders | 71 | 11 | 81.1 (70.0–90.1) | 0.75 (0.41–1.37) | 0.72 (0.39–1.33) |
| Vasculitis | 43 | 5 | 86.8 (74.3–95.6) | 0.56 (0.23–1.37) | 0.53 (0.22–1.30) |
| Miscellaneous | 147 | 20 | 84.2 (77.3–90.1) | 0.70 (0.44–1.11) | 0.70 (0.44–1.11) |
| Unknown | 244 | 42 | 78.7 (72.6–84.3) | 0.91 (0.65–1.28) | 0.90 (0.64–1.26) |
| Time with a functioning graft before reaching age 18 years[f] | | | | | |
| <5 years | 1230 | 221 | 78.7 (76.1–81.2) | 1.03 (0.85–1.25) | 1.08 (0.79–1.48)[a,b] |
| ≥5 years | 1167 | 205 | 79.1 (76.4–81.6) | 1 (ref) | 1 (ref)[a,b] |

[a]Fifteen patients had unknown age at the time of kidney transplantation.
[b]Sixty-eight patients had unknown type of kidney transplant at age 18 years.
[c]Adjusted for sex, PRD and country.
[d]Adjusted for sex, PRD, age at kidney transplantation and country.
[e]Adjusted for sex and country.
[f]Adjusted for sex, PRD, type of kidney donor, age at kidney transplantation and country.
HUS, haemolytic uremic syndrome.
Bold values represent factors that were statistically significantly associated with graft failure.

in characteristics of adult survivors of childhood KRT is likely associated with changes in the paediatric KRT population, with very young patients increasingly accepted into KRT programmes and surviving on dialysis until reaching the minimum weight for kidney transplantation [8, 10, 21]. There was also an increase in the proportion of adult survivors reaching their 18th birthday with a functioning kidney transplant, including pre-emptive grafts, compared with 1985–2004 (Supplementary data, Table S2) [2]; this was concomitant with a decrease in peritoneal dialysis as initial treatment. In the USA, the proportion of prevalent adult survivors of childhood KRT with a functioning kidney transplant also increased [22]. These results reflect the successful efforts to improve paediatric KRT care and kidney allocation policies aiming to reduce waiting times and to provide access to high-quality kidneys for paediatric patients [21–24].

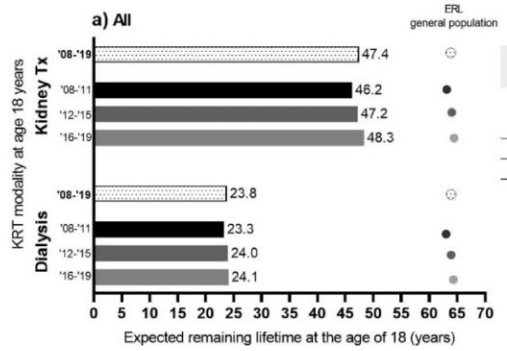
## Patient outcomes

KRT modality at age 18 years and cumulative time on dialysis during childhood were associated with patient outcomes during early adulthood. Most adult survivors of childhood KRT with a kidney graft at age 18 years had a functioning graft 5 years later (84%), whereas only about half of the adult survivors on dialysis had undergone kidney transplantation by their 23rd birthday (55%). Mortality was more than five times higher in adult survivors of childhood KRT on dialysis compared with kidney transplant recipients. Similar to results of previous studies, the longer the dialysis vintage, the higher the mortality risk among adult survivors of childhood KRT [5, 25]. Nevertheless, it is likely that patients reaching adulthood on dialysis had more comorbidities, which presumably was the reason why they were unable to receive a kidney transplant and spent more time on dialysis, demonstrating a selection bias reflected in a higher risk of death among dialysis patients compared with kidney transplant recipients [9]. In addition, HLA sensitization which may hinder (re)transplantation might be a reason for being treated with dialysis at age 18 years [26]. Unfortunately, data on comorbidities and HLA sensitization were not reported to the ERA Registry so we were unable to study this in detail.

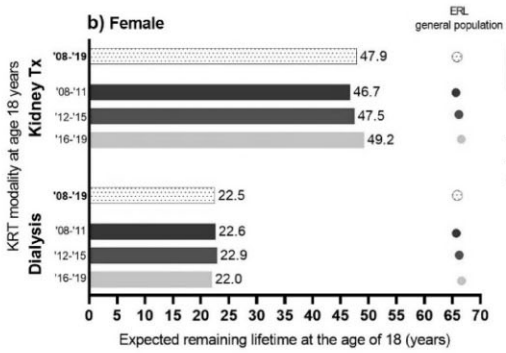
Five-year patient survival remained good at 96.9% (95% CI 96.2–97.5), but did not appear to increase after 2004, perhaps reaching its ceiling [2, 8]. However, survival among adult survivors who initiated KRT between 0–4 years of age improved, reflecting advances in the care of very young KRT patients [2, 21, 24]. Nonetheless, it would be interesting to investigate the prognosis of this patient group with longer follow-up periods.

For kidney transplant recipients, 5-year unadjusted graft survival probability from age 18 years onwards was lower than for ages 13 and 23 years (Supplementary data, Table S4). This is consistent with other studies suggesting a peak in graft failure

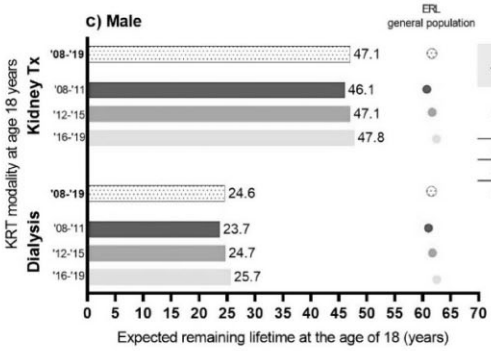
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| Year period | General population ERL, years | Kidney Tx patients ERL, years (%)* | Kidney Tx patients Life years lost (%)* | Dialysis patients ERL, years (%)* | Dialysis patients Life years lost (%)* |
|---|---|---|---|---|---|
| **2008-2019** | **64.0** | **47.4 (74)** | **16.6 (26)** | **23.8 (37)** | **40.3 (63)** |
| 2008-2011 | 63.4 | 46.2 (73) | 17.2 (27) | 23.3 (37)) | 40.1 (63) |
| 2012-2015 | 64.1 | 47.2 (74) | 16.9 (26) | 24.0 (37) | 40.1 (63) |
| 2016-2019 | 64.6 | 48.3 (75) | 16.3 (25) | 24.1 (37) | 41.0 (63) |




| Year period | General population ERL, years | Kidney Tx patients ERL, years (%)* | Kidney Tx patients Life years lost (%)* | Dialysis patients ERL, years (%)* | Dialysis patients Life years lost (%)* |
|---|---|---|---|---|---|
| **2008-2019** | **66.1** | **47.9 (72)** | **18.2 (28)** | **22.5 (34)** | **43.6 (66)** |
| 2008-2011 | 65.8 | 46.7 (71) | 19.1 (29) | 22.6 (34) | 43.2 (66) |
| 2012-2015 | 66.2 | 47.5 (72) | 18.7 (28) | 22.9 (35) | 43.3 (65) |
| 2016-2019 | 66.5 | 49.2 (74) | 17.3 (26) | 22.0 (33) | 44.5 (67) |




| Year period | General population ERL, years | Kidney Tx patients ERL, years (%)* | Kidney Tx patients Life years lost (%)* | Dialysis patients ERL, years (%)* | Dialysis patients Life years lost (%)* |
|---|---|---|---|---|---|
| **2008-2019** | **61.7** | **47.1 (76)** | **14.6 (24)** | **24.6 (40)** | **37.1 (60)** |
| 2008-2011 | 61.0 | 46.1 (76) | 14.9 (24) | 23.7 (39) | 37.3 (61) |
| 2012-2015 | 61.9 | 47.1 (76) | 14.8 (24) | 24.7 (40) | 37.2 (60) |
| 2016-2019 | 62.4 | 47.8 (77) | 14.5 (23) | 25.7 (41) | 36.7 (59) |

Abbreviations: KRT – Kidney replacement therapy; Tx - Transplantation; ERL – Expected remaining lifetime;
*The percentages indicate the percentage of ERL that KRT patients reach/lose when comparing with the general population at the same age and, when applicable, same sex.

**Figure 4:** Expected remaining lifetimes of dialysis and kidney transplant patients at age 18 years, and of the general population at the same age, by period when reaching age 18 years between 2008 and 2019, overall (**a**) and stratified by sex (**b** and **c**).

rates during adolescence/young adulthood, concomitant with the transfer from paediatric to adult nephrology care [1–3], which emphasize the importance of studying factors associated with graft loss at this age [1].

## Expected remaining lifetime

In 2008–19, the expected remaining lifetime of 18-year-old kidney transplant recipients increased, while it remained consistently lower and did not change over time for dialysis patients. Compared with kidney transplant recipients, being on dialysis at age 18 years seems to have an increased life-shortening effect on young adults. Nevertheless, kidney transplant recipients still had a lower expected remaining lifetime than age-matched persons in the general population.

Compared with the previous report, there was a slight improvement in the expected remaining lifetime of 18 year olds on dialysis, which was greater for males [2] (Supplementary data, Fig. S2). In 2008–19, 18-year-old females, particularly those on dialysis, had a shorter expected remaining lifetime than males. Vogelzang *et al.* reported that women on KRT had a higher rate of infection-related death than men, particularly young dialysis patients (aged 0–39 years) [18]. Non-compliance among young females may be related to concerns with side-effects of immunosuppressive medications such as acne, hirsutism and facial swelling, leading to higher graft failure risk and consequently shorter life expectancy [27]. However, this notion is contradicted by higher mortality rates among men in older age groups [28], so the reasons for the shorter life expectancy among 18-year-old females compared with males remain unclear. It is noteworthy that the expected remaining lifetime of 18-year-old KRT patients was based on data from all KRT patients, with different distribution of PRDs and comorbidities.

## Strengths and limitations

This study reports on one of the largest cohorts studied to date, with almost 3000 adult survivors of childhood KRT from multiple countries over a decade. Providing novel epidemiological data on this challenging patient group going through a sensitive

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period of transition from paediatric to adult nephrology care. Nevertheless, some limitations should be considered when interpreting the study findings. Data that may be important when studying outcomes in adult survivors of childhood KRT, including comorbidities and clinical data such as estimated glomerular filtration rate or residual kidney function, are not part of the ERA Registry dataset. Additionally, mainly patients from Western Europe were included in this study, and the findings might not be generalizable to Eastern Europe.

## Conclusion

Already at age 18 years, kidney transplant recipients had a shorter life expectancy than the general population. About one-fifth of kidney grafts failed between ages 18 and 23 years. Graft survival probability was significantly lower among 18 year olds compared with kidney recipients 5 years younger and older. Nevertheless, health outcomes of kidney transplant recipients were better than for 18 year olds on dialysis. Our results highlight the impact of this sensitive period on patient health, and reinforce the importance of investigating the effect of the transition from paediatric to adult KRT care on patient outcomes, particularly graft survival. KRT treatment at age 18 years and dialysis vintage before reaching adulthood were associated with 5-year patient survival. Healthcare policies should aim to reduce time on dialysis during childhood by continuing efforts to improve paediatric kidney allocation policies. Moreover, the unclear reasons for shorter life expectancy among 18-year-old females compared with males warrant further study.

## SUPPLEMENTARY DATA

Supplementary data are available at *Nephrology Dialysis Transplantation* online.

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## AUTHORS' CONTRIBUTIONS

Conceptualization: I.R.M.S., M.B., A.K., V.S.S., K.J.J.; methodology: I.R.M.S., M.B., A.K., V.S.S., K.J.J.; formal analysis: I.R.M.S.; writing–original draft: I.R.M.S., M.B., A.K., V.S.S., K.J.J.; writing–review and editing: F.A.O., F.C.O., H.R., J.H., J.W.G., K.H., L.B., M.S., M.A., R.P., S.B., S.T.-A., S.A.B., S.S.S., A.O.; all authors read and approved the final manuscript.

## DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared with any third party because the national and regional registries that provided data to the ERA Registry remain the owners of the data.

## CONFLICT OF INTEREST STATEMENT

We have no conflicts of interest to declare.

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