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► **To cite this version:**

Henna Kaijansinkko, Marjolein Bonthuis, Kirsi Jahnukainen, Jerome Harambat, Enrico Vidal, et al.. Clinical outcomes of pediatric kidney replacement therapy after childhood cancer-An ESPN/ERA Registry study. American Journal of Transplantation, 2024, Online ahead of print. 10.1016/j.ajt.2024.11.002 . hal-04836547

**HAL Id: hal-04836547**

**<https://hal.science/hal-04836547v1>**

Submitted on 13 Dec 2024

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Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: [www.amjtransplant.org](http://www.amjtransplant.org)

Original Article

# Clinical outcomes of pediatric kidney replacement therapy after childhood cancer—An ESPN/ERA Registry study

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**Abbreviations:** BP, blood pressure; DD, deceased donor; ESKD, end-stage kidney disease; ESPN/ERA, European Society for Paediatric Nephrology/European Renal Association; GDP, gross domestic product; HSCT, hematopoietic stem cell transplantation; KT, kidney transplantation; KRT, kidney replacement therapy; LFU, loss to follow-up; PRD, primary renal disease; SDS, standard deviation scores; WT, Wilms tumor.

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<https://doi.org/10.1016/j.ajt.2024.11.002>

Received 22 April 2024; Received in revised form 16 October 2024; Accepted 1 November 2024

Available online xxx

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## ARTICLE INFO

### Keywords:

children

cancer

kidney replacement therapy

kidney transplantation

malignancy

mortality

## ABSTRACT

Cancer and its treatment may lead to kidney injury and the need for kidney replacement therapy (KRT). We identified 287 pediatric KRT patients with a history of malignancy from the European Society for Paediatric Nephrology/European Renal Association Registry. Of these, 197 had cancer as a primary cause of KRT (group 1) and 90 had a malignancy diagnosis before KRT (group 2). Two matched controls without malignancy were randomly selected for each patient. Data were complemented with a questionnaire. Median time to kidney transplantation (KT) from KRT initiation was 2.4 (IQR: 1.5-4.7), 1.5 (IQR: 0.4-3.3), 3.6 (IQR: 1.3 to Q3 not reached), and 1.1 (IQR: 0.3-3.6) years for group 1, their controls, group 2, and their controls, respectively. Overall 10-year mortality for those on KRT was higher among cancer patients vs controls in group 1: 16% vs 9% (adjusted hazard ratio 2.02, 95% CI: 1.21-3.37) and in group 2: 23% vs 14% (adjusted hazard ratio 2.32, 95% CI: 1.11-4.85). In contrast, 10-year patient survival after the first KT was comparable to controls (93% vs 96%; 100% vs 94%, in groups 1 and 2, respectively). In summary, childhood cancer survivors' KT was delayed, and their overall mortality when on KRT was increased, but once transplanted, their long-term outcome was similar to other KT recipients.

## 1. Introduction

Pediatric cancer patients' survival has improved significantly; eg, since the late 1970s, 5-year survival for Wilms tumor (WT) patients has increased from approximately 75% to over 90%.<sup>1-3</sup> This has resulted in increasing numbers of childhood cancer survivors with various treatment-related late effects. The most common late effects are cardiopulmonary-related including hypertension, endocrine-related including altered growth, metabolism, and fertility, and those related to second primary malignancies.<sup>4-9</sup> End-stage kidney disease (ESKD) is a relatively rare but burdensome late effect.<sup>10-12</sup>

Childhood cancer may lead to ESKD by different mechanisms.<sup>13-15</sup> The tumor, or its resection, may result in permanent kidney damage and reduced nephron mass. ESKD may develop soon after the primary cancer diagnosis or progress more slowly over the following years. In such patients, cancer is considered the primary renal disease (PRD) and the reason for kidney replacement therapy (KRT). Further, irradiation or cancer chemotherapy including cisplatin, ifosfamide, or methotrexate, especially in combination with nephrotoxic antimicrobials, may

cause kidney injury. Thrombotic microangiopathy commonly seen in hematopoietic stem cell transplantation (HSCT) may also result in kidney injury.<sup>16</sup> These cancer treatments alone or together with another kidney disease may result in ESKD. Cancer therapy can precede ESKD by years or decades and it may sometimes be difficult to recognize the specific cause of kidney failure.<sup>11</sup>

Only a few reports on KRT after childhood cancer are available<sup>14,17-20</sup> and most comprise WT patients exclusively.<sup>14,17-19</sup> Except for the oldest case series from the 1970s, all later studies have reported similar results: increased early mortality among progressive bilateral WT patients, but thereafter similar patient and graft survival compared to other kidney transplantation (KT) recipients.<sup>14,19,20</sup> Recent outcome data in large cohorts with matched controls are lacking and current knowledge about patients with malignancies other than WT is very limited.

The aim of this European Society for Paediatric Nephrology/European Renal Association (ESPN/ERA) Registry study was to evaluate outcomes of KRT, ie, access to KT, survival of those on KRT and after KT, causes of death, and graft survival in KRT patients after childhood cancer. Additionally, we studied growth, hypertension, and the incidence of second primary malignancies.

## 2. Materials and methods

### 2.1. Data source and patient population

Data were collected within the framework of the population-based ESPN/ERA Registry. Annually, the registry collects individual patient data on all European children requiring KRT. Children are followed from the start of KRT until transfer to adult nephrology care, recovery of kidney function, loss to follow-up (LFU), or death.<sup>21</sup> For the present analysis, we included all patients for whom a history of malignancy was reported at KRT initiation and who commenced KRT <20 years of age between 1980 and 2019. For each patient with cancer, 2 matched controls without malignancy were selected. Matching was done through the SAS procedure “proc surveyselect” using random sampling without replacement. This procedure uses equal probability sampling hence, every patient in the sample has an equal probability of being selected. Cancer patients were matched on a composite index variable consisting of age at KRT initiation (2-year age bands), sex (male or female), year of KRT, and gross domestic product (GDP) (low [ $<10\,000$  USD], middle [ $10\,000$ - $30\,000$  USD] or high [ $>30\,000$  USD] income).<sup>22-24</sup>

Patients from the following 25 countries were included: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Norway, Poland, Portugal, Russia, Serbia, Spain, Sweden, Switzerland, the Netherlands, Türkiye, Ukraine, and the United Kingdom. The Medical Ethics Review Committee of the Amsterdam Medical Center, the Netherlands provided a waiver for ethical approval of this study (W21\_257# 21.283). For the analyses, we divided patients into 2 groups: patients with cancer as PRD (group 1) and patients with a history of malignancy at KRT start for whom particular kidney diagnoses were reported as cause of ESKD (group 2). A total of 287 patients starting KRT after cancer treatment were identified: 197 in group 1 and 90 in group 2. Data on the course of KRT, such as the date of KT, graft failure and patient death were available for all patients. However, data on growth and blood pressure (BP) are collected on a voluntary basis and are not available for every patient. A detailed description of the ESPN/ERA Registry can be found elsewhere.<sup>25</sup> Because the ESPN/ERA Registry is a KRT registry, the availability of malignancy-related variables was limited. Therefore, we distributed a questionnaire to each country reporting cancer patients and data were received for 53% of patients, with similar patient characteristics as patients for whom no questionnaire was returned. Among others, the questionnaire included questions, on the exact cancer diagnosis, its treatment, relapses and second primary malignancies occurring after KRT initiation. The full questionnaire can be found in the [Supplementary Material](#).

### 2.2. Definition of variables

Due to low patient numbers per country, cancer patients were matched to controls on the level of country macro-economic indicators, ie, GDP per capita,<sup>26</sup> and divided into low-income, medium-income, and high-income countries. Height was

expressed as standard deviation scores (SDS) based on national or European growth charts.<sup>27</sup> Systolic and diastolic BP SDS were calculated according to age-adjusted, sex-adjusted, and height-adjusted values defined by the National High Blood Pressure Education Program Working Group Fourth report.<sup>28</sup> PRD and causes of death were categorized according to the ERA Registry coding system. Cardiac failure, cardiac arrest/sudden death, myocardial ischemia and infarction, and cerebrovascular accident were combined as cardiovascular mortality.<sup>29</sup> Cancer treatment intensity was scored according to the Intensity of Treatment Rating scale 2.0 (ITR-2).<sup>30</sup> Briefly, this scoring system aims to classify cancer treatment intensity into 4 categories (least intensive, moderate, very intensive, and most intensive) based on chemotherapy, need for surgery, irradiation therapy, and HSCT.

### 2.3. Statistical analyses

Time to first KT within 5 and 10 years of KRT initiation was analyzed based on the time between KRT initiation and the first KT date. The cumulative incidence competing risk method was applied to calculate unadjusted time to first KT, taking into account the competing risk of death. Cox proportional hazards analysis was performed to examine the associations between cancer history and time to first KT, patient, and graft survival, adjusting for potential confounders and a frailty term accounting for the clustering effect of matched pairs of cancer patients and controls. The following confounders were adjusted for whenever appropriate: country, age, sex, PRD, and donor type (living or deceased donor [DD]). Graft survival was defined as being alive with a functioning graft and calculated as time since the first KT. Unadjusted patient survival after KRT and KT is shown in Kaplan-Meier plots. Patients were followed until death, LFU, or end of study (December 31, 2019). Linear mixed model regression analyses were applied to model longitudinal data of height and BP SDS with both a random intercept and slope at the level of matched pairs and an unstructured covariance structure as each patient trajectory is unique (ie, number and timing of measurements).  $P$  values  $< .05$  were considered statistically significant. All statistical analyses were performed in SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

## 3. Results

### 3.1. Patient characteristics

Patients with cancer as the primary cause for KRT (group 1) were younger (median age 4.2; IQR: 1.7-8.5 years) at KRT initiation compared to cancer patients with other PRDs (group 2) (median 11.7; IQR: 5.5-15.6 years) (Tables 1 and 2). Median (IQR) follow-up time from KRT initiation was 6.4 (2.1-12.8) years in group 1 and 3.4 (1.1-7.9) years in group 2. All patients in group 1 and none in group 2 had a kidney tumor. Cancer type was reported for all patients in group 1 and for 40% of group 2 patients; in the latter, approximately half of the cases were lymphomas or leukemias (Table 3). According to the IRT-2 scale, 43% of patients in group 1 and only 7% in group 2 had received

**Table 1**

Characteristics of patients with cancer as PRD (group 1) and their controls matched for age, sex, year of KRT, and country macro-economics.

Patient characteristics	Cancer as PRD	
	Group 1	Controls
	N = 197	N = 394
Age at the start of KRT, median (IQR)	4.2 (1.7-8.5)	4.2 (1.8-8.8)
0-4 y	114 (57.9%)	228 (57.9%)
5-9 y	40 (20.3%)	79 (20.1%)
10-14 y	23 (11.7%)	47 (11.9%)
15-19 y	20 (10.2%)	40 (10.2%)
% Males	39.6%	39.6%
Treatment at the start of KRT <sup>a</sup>		
HD	119 (60.4%)	113 (28.7%)
PD	56 (28.4%)	192 (48.7%)
KT	14 (7.1%)	70 (17.8%)
Missing/Unknown	8 (4.1%)	19 (4.8%)
Period of starting KRT		
1980-1989	16 (8.1%)	33 (8.4%)
1990-1999	22 (11.2%)	43 (10.9%)
2000-2009	69 (35.0%)	138 (35.0%)
2010-2018	90 (45.7%)	180 (45.7%)
Macro-economics (GDP)		
Low-income countries (<10 000 USD)	26 (13.2%)	52 (13.2%)
Medium-income countries (10 000-30 000 USD)	26 (13.2%)	52 (13.2%)
High-income countries (>30 000 USD)	145 (73.6%)	290 (73.6%)
PRD		
Cancer	197 (100%)	0 (0%)
Glomerulonephritis		82 (20.8%)
CAKUT		119 (30.2%)
Cystic kidney disease		50 (12.7%)
Hereditary nephropathy		39 (9.9%)
Ischemic renal failure		6 (1.5%)
HUS		25 (6.4%)
Metabolic disorders		8 (2.0%)
Vasculitis		9 (2.3%)
Miscellaneous		27 (6.9%)
Missing/unknown		29 (7.4%)

CAKUT, congenital anomalies in the kidneys and urinary tract; GDP, gross domestic product; HD, hemodialysis; HUS, hemolytic uremic syndrome; KRT, kidney replacement therapy; KT, kidney transplantation; PD, peritoneal dialysis; PRD, primary renal disease; USD, US dollar.

**Table 2**

Characteristics of patients with a history of malignancy at the start of KRT (group 2) and their controls matched for age, sex, year of KRT, and country macro-economics.

Patient characteristics	History of malignancy at the start of KRT	
	Group 2	Controls
	N = 90	N = 180
Age at the start of KRT, median (IQR)	11.7 (5.5-15.6)	11.8 (5.7-15.3)
0-4 y	20 (22.2%)	40 (22.2%)
5-9 y	18 (20.0%)	33 (18.3%)
10-14 y	27 (30.0%)	57 (31.7%)
15-19 y	25 (27.8%)	50 (27.8%)
% Males	47.8%	47.8%
Treatment at the start of KRT <sup>a</sup>		
HD	53 (58.9%)	69 (38.3%)
PD	27 (30.0%)	64 (35.6%)
KT	9 (10.0%)	36 (20.0%)
Missing/unknown	1 (1.1%)	11 (6.1%)
Period of starting KRT		
1980-1989	1 (1.1%)	2 (1.1%)
1990-1999	12 (13.3%)	24 (13.3%)
2000-2009	25 (27.8%)	50 (27.8%)
2010-2018	52 (57.9%)	104 (57.9%)
Macro-economics (GDP)		
Low-income countries (<10 000 USD)	12 (13.3%)	24 (13.3%)
Medium-income countries (10 000-30 000 USD)	17 (18.9%)	34 (18.9%)
High-income countries (>30 000 USD)	61 (67.8%)	122 (67.8%)
PRD		
Glomerulonephritis	13 (14.4%)	32 (17.8%)
CAKUT	14 (15.6%)	62 (34.4%)
Cystic kidney disease	4 (4.4%)	26 (14.4%)
Hereditary nephropathy	3 (3.3%)	8 (4.4%)
Ischemic renal failure	8 (8.9%)	6 (3.3%)
HUS	4 (4.4%)	8 (4.4%)
Metabolic disorders	2 (2.2%)	4 (2.2%)
Vasculitis	0 (0.0%)	3 (1.7%)

(continued on next page)

**Table 2** (continued)

Patient characteristics	History of	Controls
	malignancy	
	at the start	
	of KRT	
	Group 2	
	N = 90	N = 180
Miscellaneous	36 (40.0%) <sup>b</sup>	16 (8.9%) <sup>c</sup>
Missing/unknown	6 (6.7%)	15 (8.3%)

CAKUT, congenital anomalies in the kidneys and urinary tract; GDP; gross domestic product; HD, hemodialysis; HUS, hemolytic uremic syndrome; KRT, kidney replacement therapy; KT, kidney transplantation; PD, peritoneal dialysis; USD, US dollar.

<sup>a</sup> Statistically significant difference between patients with malignancy and their controls.

<sup>b</sup> Miscellaneous included tubulointerstitial disorders (N = 24, of which 20 were drug-induced [among others cisplatin]) and other (unspecified) renal disorders (N = 12).

<sup>c</sup> Including tubulointerstitial disorders (N = 7) and other (unspecified) renal disorders (N = 9).

least intensive treatments, whereas 57% in group 1 vs 94% of patients in group 2 had received moderate to very intensive treatments (Table 3). Compared with patients in group 1, more children in group 2 had received irradiation as conditioning regimen in HSCT (Table 3).

### 3.2. Treatment modality, time to KT, and graft survival

Treatment modality at KRT initiation differed between childhood cancer survivors and controls. Cancer patients started KRT more often on hemodialysis (60.4% vs 28.7% in group 1; and 58.9% vs 38.3% in group 2) (Tables 1 and 2) and underwent preemptive KT less often compared with matched controls (7.1% vs 17.8% in group 1, 10.0% vs 20.0% in group 2).

Time to KT was longer in both cancer groups compared to their controls. However, data on listing for transplantation were unavailable. Significantly fewer patients in group 1 (81.4%) had received KT (adjusted hazard ratio (HR) of 0.74, 95% CI: 0.60-0.91) compared to their controls (88%) up to 10 years following KRT commencement, mostly due to higher mortality (Fig. 1A). The majority of patients received a DD KT, 57% in group 1 and 64% of their controls. At 10 years' follow-up, 11% of patients in group 1 and 6% of their controls had died before first KT. In group 1, 7 (3.6%) of patients did not receive a KT during the study period because of LFU, whereas this was the case for 21 (5.3%) of their controls. In group 2, 14 patients (15.5%) were lost to follow-up before receiving a KT (23 [12.8%] of their controls), resulting in significantly fewer patients who had received a KT at 10 years after KRT initiation (67%; 60% from a DD) compared to their controls (93%; 55% from a DD) (adjusted HR of 0.53, 95% CI: 0.36-0.77) (Fig. 1B). All deaths (23%) in group 2 were before first KT, whereas mortality before first KT was 7% in their controls. Median time to KT from KRT start was 2.4 years (IQR: 1.5-4.7) in

group 1 vs 1.5 years (IQR: 0.4-3.3) in controls, whereas this was 3.6 years (IQR: 1.32 to Q3 not reached) in group 2 vs 1.1 years (IQR: 0.3-3.6) in their controls.

Ten-year graft survival did not differ significantly between cancer survivors and controls, it being 76%, 74% ( $P = .99$ ), 66%, 76% ( $P = .68$ ) in group 1, their controls, group 2, and their controls, respectively. Consequently, risk of graft loss did also not differ between groups (adjusted HR group 1 vs controls: 0.95, 95% CI: 0.58-1.55; adjusted HR group 2 vs controls: 1.08, 95% CI: 0.42-2.81). Similar results were obtained for death-censored graft loss (adjusted HR group 1 vs controls: 0.97, 95% CI: 0.58-1.61; adjusted HR group 2 vs controls: 1.54, 95% CI: 0.56-4.21).

### 3.3. Overall patient survival

Overall mortality was higher in cancer patients than in their matched controls. One-year mortality after KRT start was 10%, 4%, 10%, and 3% in group 1, their controls, group 2, and their controls, respectively. At 10 years after KRT initiation, unadjusted patient survival was significantly lower, 84% in group 1 compared to 91% in their controls (Fig. 2A;  $P = .006$ ; adjusted HR: 2.02, 95% CI: 1.21-3.37). Cause of death was available for 81% of patients in group 1, with cancer relapse being the leading cause of death (Table 4).<sup>29</sup> In group 2, the unadjusted 10-year patient survival was also significantly lower (77%) compared to controls (86%,  $P = .015$ ; Fig. 2B), and remained statistically significant after adjustment for GDP, age, sex, and PRD (adjusted HR: 2.32, 95% CI: 1.11-4.85). Information about causes of death was unavailable for most patients in group 2 (Table 5).<sup>29</sup>

### 3.4. Survival after KT

Ten-year patient survival after the first KT did not differ significantly between group 1 (93%) and their controls (96%,  $P = .45$ ; Fig. 2C) or between group 2 (100%) and their controls (94%,  $P = .21$ ; Fig. 2D).

### 3.5. Cancer relapses and secondary malignancies after KRT

Data regarding cancer relapses were available for 91 (46%) patients in group 1 and for 27 (30%) group 2 patients. With respect to second primary malignancies, available numbers were 87 (44%) and 25 patients (28%) in group 1 and group 2, respectively. Altogether 18 patients in group 1 and 6 patients in group 2 had a relapse of their primary cancer (approximately 20% of patients in both groups with known outcomes) (Table 3). All relapses occurred before the first KT. Second primary malignancies were diagnosed in 7 patients in group 1 and 1 patient in group 2.

### 3.6. Growth and BP

Unadjusted height SDS did not differ between cancer survivors and controls over the 10-year follow-up after KRT (Fig. 3A, B). Height SDS for cancer survivors tended to decrease from KRT initiation to 10-year follow-up, and however, was not statistically significant. The majority of group 2 patients showed growth

**Table 3**

Cancer and treatment characteristics reported by questionnaire. Cancer treatment intensity was scored according to ITR-2.

Cancer and treatment characteristics	Cancer as PRD (group 1)	History of malignancy (group 2)	P value
Classification cancer diagnosis	(N = 113; 57% of all cases)	(N = 36; 40% of all cases)	<.001
Leukemias	-	10 (28%)	
Lymphomas	-	6 (17%)	
CNS Neoplasms	-	3 (8%)	
Neuroblastomas	-	3 (8%)	
Kidney tumors	113 (100%)	-	
Malignant bone tumors	-	6 (17%)	
Soft tissue sarcomas	-	2 (6%)	
Germ cell tumors	-	5 (14%)	
Classification tumor stages	(N = 53; 27% of all cases)	(N = 16; 18% of all cases)	
1	12 (23%)	1 (6%)	<.001
2	9 (17%)	2 (13%)	
3	12 (23%)	6 (38%)	
4 (metastatic)	20 (38%)	3 (19%)	
Leukemia risk low	-	1 (6%)	
Leukemia risk intermediate	-	2 (13%)	
Leukemia risk high	-	-	
Nephrectomy	(N = 104; 52% of all cases)	(N = 26; 29% of all cases)	
No	3 (3%)	23 (89%)	<.001
Bilateral	71 (69%)	0 (0%)	
Unilateral/partial	28 (27%)	3 (12%)	
Unknown type of nephrectomy	2 (2%)		
Cancer treatment			
Chemo	(N = 100; 51% of all cases)	(N = 31; 34% of all cases)	.06
Yes	92 (92%)	25 (81%)	
No	8 (8%)	6 (19%)	
Irradiation	(N = 92; 47% of all cases)	(N = 30; 33% of all cases)	.17
Yes	25 (27%)	9 (30%)	
No	67 (73%)	21 (70%)	
Hematopoietic stem cell transplantation	(N = 95; 48% of all cases)	(N = 31; 34% of all cases)	.01
Yes	1 (1%)	4 (13%)	
No	94 (99%)	27 (87%)	
Intensity of treatment rating	(N = 81; 41%)	(N = 31; 34%)	<.01
1 (least intensive treatments)	35 (43%)	2 (7%)	
2 (moderately intensive treatments)	1 (1%)	11 (36%)	
3 (very intensive treatments)	41 (51%)	11 (36%)	
4 (most intensive treatments)	4 (5%)	7 (23%)	
Median (IQR)	3 (1; 3)	3 (2; 3)	
Cancer relapses <sup>a</sup>	(N = 91; 46%)	(N = 27; 30%)	.20

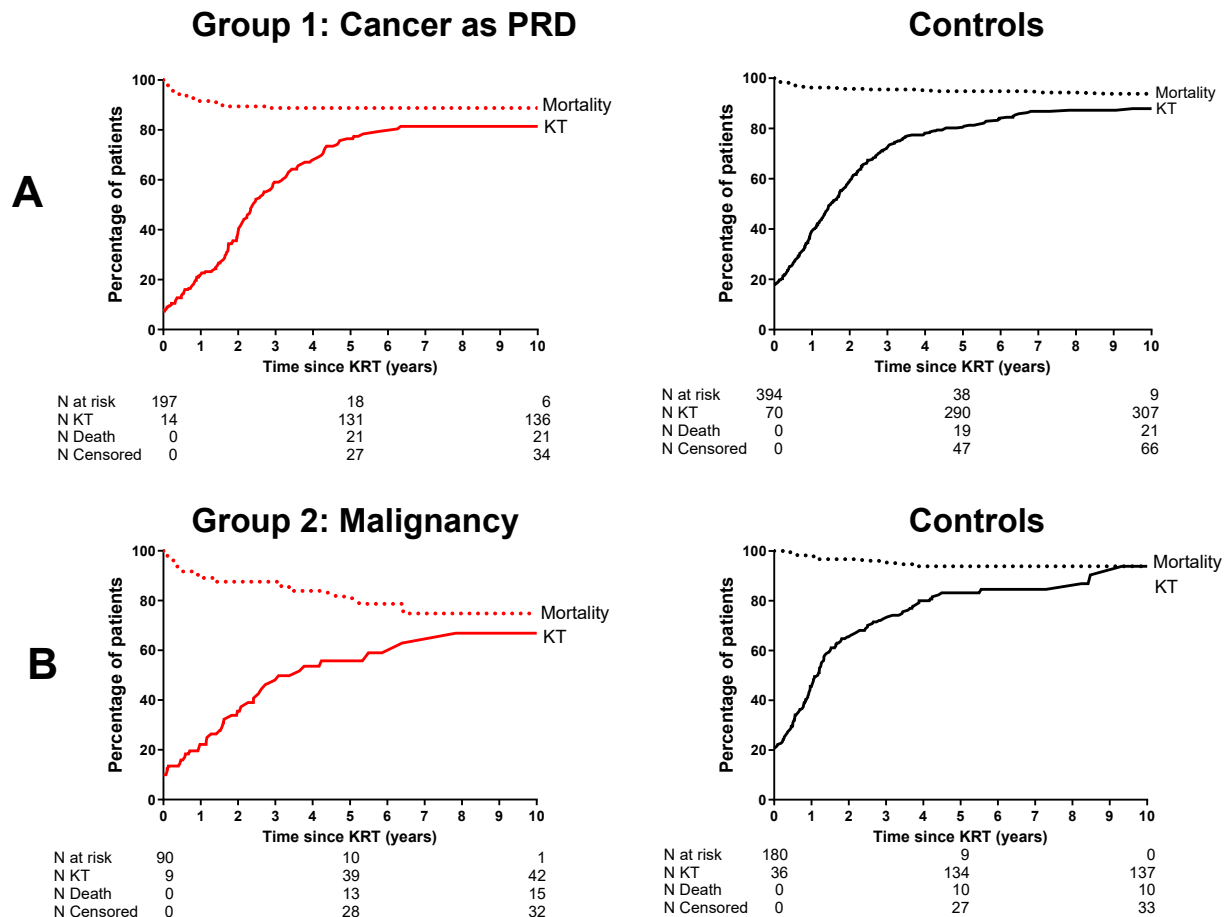
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Table 3 (continued)

Cancer and treatment characteristics	Cancer as PRD (group 1)	History of malignancy (group 2)	P value
Yes	18 (19.8%)	6 (22%)	.31
No	73 (80%)	21 (78%)	
Second malignancies	(N = 87; 44%)	(N = 25; 28%)	
Yes	7 (8%)	1 (4%)	
No	80 (92%)	24 (96%)	

CNS, central nervous system; ITR-2, Intensity of Treatment Rating scale 2.0; PRD, primary renal disease.

<sup>a</sup> Relapse diagnoses were CNS tumor 2, osteosarcoma 1, leukemia 1, neuroblastoma 1, and rhabdomyosarcoma 1.



**Figure 1.** Cumulative incidence of receiving a kidney transplant for patients with cancer as a primary renal disease (PRD) and their matched controls (A) and for patients with a diagnosis of malignancy before kidney replacement therapy (KRT) start and their matched controls (B) in the first 10 years after KRT initiation. KT, kidney transplantation.

retardation at the end of follow-up. The unadjusted systolic and diastolic BP SDS did not differ between cancer survivors and controls over the 10-year follow-up after KRT (Fig. 4). Group 1 patients as well as their controls had higher systolic and diastolic BP SDS at KRT initiation compared to 10-year follow-up ( $P < .001$ ). For group 2 patients this trend was only noticed for the diastolic BP SDS ( $P = .002$ ), whereas no trends were observed for controls.

#### 4. Discussion

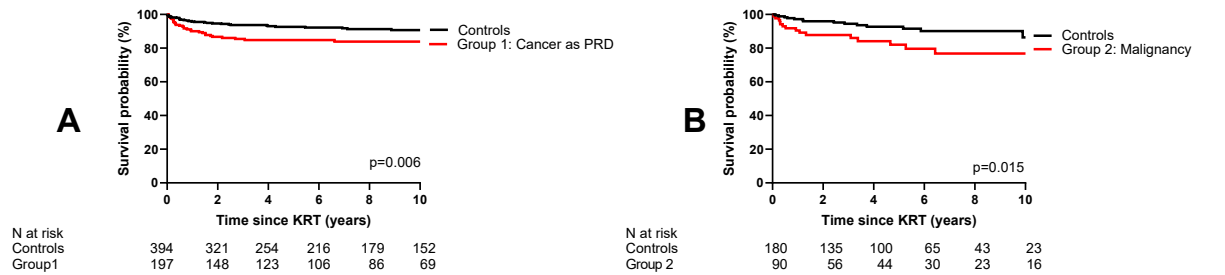
The present study offers novel insights into the outcomes of KRT following childhood cancer. Childhood cancer survivors

experienced delayed time to KT and their overall survival was decreased compared with peers receiving KRT not associated with malignancy. However, when possible, KT following childhood cancer is successful and no differences in graft or post-KT patient survival were observed. To the best of our knowledge, this registry-based study is the largest study reporting outcomes of pediatric KRT after childhood cancer and includes all cancer types other than kidney tumors.

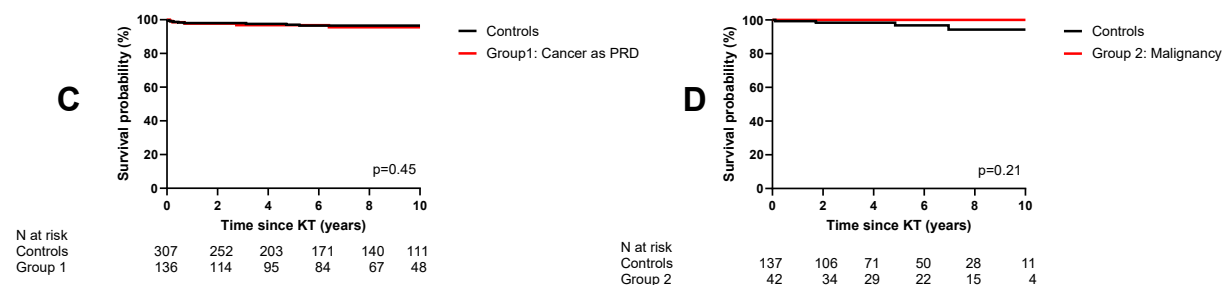
Group 1 consisted solely of kidney tumors, mainly WT, whereas in group 2, diagnoses of malignancy reflected general childhood cancer diagnoses. WT mostly affects children under 5 years,<sup>31</sup> explaining the younger age at KRT initiation among



## Patient survival after KRT



## Patient survival after KT



**Figure 2.** (A) and (B) Patient survival probability of cancer patients and their controls in the first 10 years after kidney replacement therapy (KRT) initiation. (C) and (D) Patient survival probability of cancer patients and their controls in the first 10 years after the first kidney transplantation (KT). PRD, primary renal disease.

**Table 4**

Causes of death for group 1 and controls.

Cause of death	Cancer as PRD Group 1 N = 29	Control N = 30
CVD	4 (13.8%)	6 (20.0%)
Infection	2 (6.9%)	6 (20.0%)
Malignancy	18 (62.1%)	1 (3.3%)
Other	4 (13.8%) <sup>a</sup>	7 (23.3%) <sup>b</sup>
Unknown	1(3.5%)	10 (33.3%)

Causes of death are grouped according to the ERA Registry coding system.<sup>29</sup> Causes of death differ significantly between the groups ( $P < .001$ ). CVD, cardiovascular disease; PRD, primary renal disease.

<sup>a</sup> Including cirrhosis not viral (N = 1) and cachexia (N = 1).

<sup>b</sup> Including End-stage kidney failure treatment ceased for any other reason (N = 1).

group 1 patients. Hematologic cancers comprise around 40% of childhood malignancies, which seemed to be the case in group 2 diagnoses; however, 31% of patients in group 2 had a bone or germ cell tumor which overall accounts only for <10% of all childhood cancers.<sup>32</sup> Our observations suggest an increased KRT risk in these diagnostic groups.

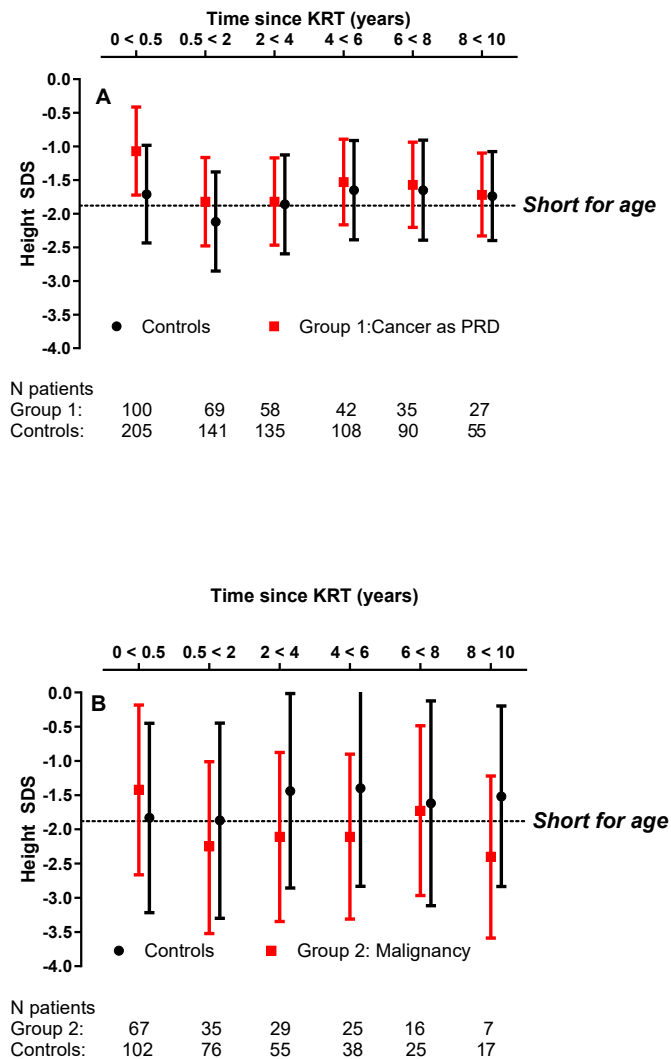
**Table 5**

Causes of death for group 2 and controls.

Cause of death	History of malignancy Group 2 N = 15	Control N = 14
CVD	3 (20.0%)	2 (14.3%)
Infection	2 (13.3%)	2 (14.3%)
Malignancy	3 (20.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)
Unknown	7 (46.7%)	10 (71.4%)

Causes of death are grouped according to the ERA Registry coding system.<sup>29</sup> CVD, cardiovascular disease.

Time to KT was significantly delayed in both cancer groups compared to their controls. This may be attributed to various factors, including the need for extensive cancer treatment before considering KT, donor availability, and concerns about cancer recurrence posttransplant. The median time to KT was 2.4 years for WT patients and 3.6 years for other cancer survivors. These data reflect the European best practice recommendations that suggest a minimum 2-year waiting period between cancer treatment and KT.<sup>33</sup> The length of the waiting period though has been questioned because especially WT patients' relapses are



**Figure 3.** (A) Unadjusted height standard deviation scores (SDS) over time since kidney replacement therapy (KRT) initiation for group 1 patients and controls. (B) Unadjusted height SDS over time since KRT initiation for group 2 patients and controls.

relatively rare after 1 year of treatment.<sup>14</sup> The present study highlights that childhood cancer survivors do not have inferior graft or patient survival after KT. Ten-year graft survival was around 70% in all groups and similar findings have been reported previously.<sup>14,19,20</sup> Although the difference is not statistically significant, in group 2, graft survival tended to be somewhat lower compared to controls. However, this may be explained by the relatively wide variation in underlying diagnoses in this group. The excellent outcomes of KT may support shortening waiting periods, at least for those cancer types with a low relapse rate or when relapses occur early.

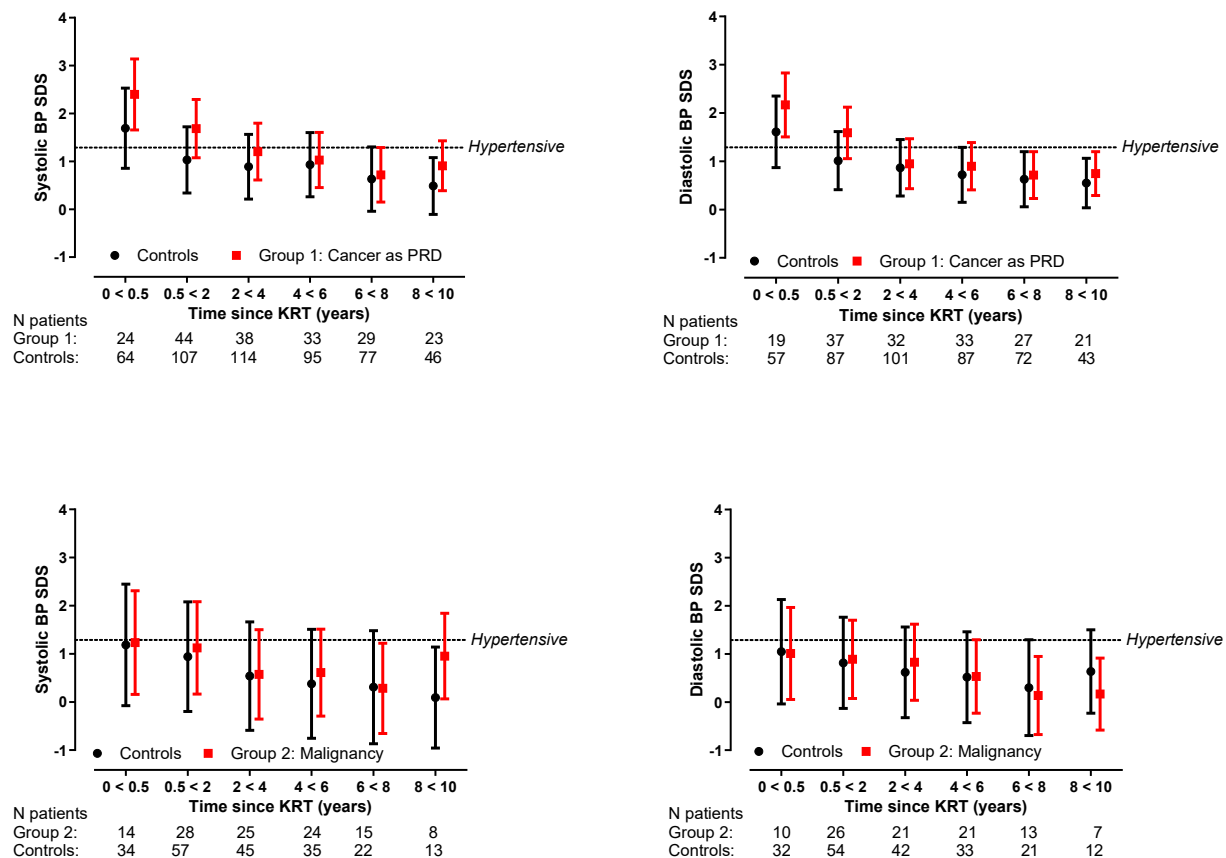
Childhood cancer survivors who are on KRT had increased mortality until they received KT, after which their survival was similar to other pediatric KT recipients. In group 1 patients, cancer relapse was the leading cause of early death. Our findings for WT outcomes are similar to the NAPRTCS registry and the National Wilms Tumor Study cohort, which reported high early mortality among bilateral WT patients,<sup>14,19</sup> although mortality did not differ

compared to controls approximately 1 year later. No previous registry-based studies have described outcomes of nonkidney cancer types in children. A study by Serrano et al<sup>20</sup> reported a case series of 7 patients with similar diagnoses as group 2 with comparable survival to KT recipients without a cancer diagnosis. In the present study, mortality in group 2 patients increased slowly over time and was significantly higher than for controls at 10-year follow-up. Unfortunately, the causes of death remained uncertain. Mortality was not increased, and cancer relapses were not observed following KT in either cancer patient group. Thus, it is fair to conclude that KT did not increase mortality following childhood cancer, and therefore, we should perhaps not be reluctant to consider KT in patients with a history of cancer. Still, conclusions from the present study need to be made with caution as patients with poor prognoses were most likely excluded from KT.

Regarding long-term complications, growth retardation was observed in group 2 patients and is a common challenge among childhood cancer survivors as well as among pediatric CKD patients.<sup>34-37</sup> Growth can be affected by ESKD itself, by immunosuppressive therapy, particularly glucocorticoids, by altered hypothalamic-pituitary function because of the tumor, surgery or irradiation, or by radiation-induced impairment of spinal growth.<sup>4,36,37</sup> In the WT group the transient growth delay, which was observed at KRT initiation, is likely due to a period of CKD and dialysis and glucocorticoid treatment after KT.<sup>36</sup> Other cancer survivors may have more fundamental growth retardation because of a longer time on dialysis, older age at transplantation, and more intensive cancer treatments including HSCT and irradiation.<sup>4,36-38</sup>

Hypertension was common at the start of KRT in group 1 patients and their controls, but the BP seemed to normalize during follow-up. Childhood cancer treatment and CKD are known risk factors for hypertension and higher cardiovascular morbidity and mortality in the long run.<sup>5,6,39,40</sup> Of pediatric KRT patients, 66% to 70% are hypertensive.<sup>39</sup> Previous cancer treatments, particularly the conditioning regimen for stem cell transplant and abdominal irradiation, may further increase the risk of hypertension.<sup>5</sup> Most patients in the WT group were young during cancer treatment and had undergone nephrectomy during early life. Lack of residual urine output and concomitant risk for hypervolemia as well as young age may explain the likelihood of hypertension,<sup>39,41</sup> whereas their risk of permanent hypertension after KT was relatively small due to the short time on dialysis. It is of note that the relatively short follow-up time of 10 years may not be sufficient to manifest cancer treatment-related risk of hypertension.<sup>7-9,39</sup> The present observations suggest that effective BP management was achieved after KRT, which is crucial for preventing cardiovascular complications in this patient group. Increased cardiovascular mortality among both KRT and childhood cancer patients underlines the need for meticulous follow-up and intervention for cardiovascular risk factors among long-term survivors.

Secondary malignancies were identified in a subset of patients. De novo malignancy is a known complication for both KT patients and childhood cancer survivors.<sup>42,43</sup> A 50-year follow-up study by Wong et al<sup>6</sup> showed that 16% of WT survivors



**Figure 4.** Unadjusted systolic (left panel) and diastolic (right panel) blood pressure (BP) standard deviation scores (SDS) over time since kidney replacement therapy (KRT) initiation for group 1, their controls, group 2, and their controls.

developed a secondary malignancy and mortality was increased compared to the reference population. In addition, there are several recent cohort studies showing increased cancer risk in both adult and pediatric KT recipients.<sup>44-46</sup> Ploos van Amstel et al<sup>42</sup> have shown that 13% and 41% of the pediatric KT recipients have malignancies after 20 and 30 years of follow-up, respectively, suggesting that the risk of cancer increases over time. This is probably due to a longer exposure to immunosuppressive drugs and oncogenic viral infections, such as Epstein-Barr Virus. The risk of secondary malignancies is also strongly related to cancer-predisposing genetic factors. Bilateral WT patients are likely to have cancer-predisposing syndrome, which may further increase their risk of second malignancy.<sup>12</sup> The magnitude of the combined risk and its effect on mortality for childhood cancer survivors on KRT still remains unclear as our data and follow-up time were not sufficient to draw conclusions. Secondary malignancy risk and mortality do not necessarily increase concurrently as Youn et al<sup>47</sup> discovered in adult heart transplant recipients with a pretransplant history of malignancy; posttransplant malignancy was diagnosed in 43.8% of patients during 8.6 years of follow-up but mortality was still equal to that of other heart transplant recipients. On the other hand, a recently published large registry-based study including both pediatric and adult solid organ transplant recipients indicated higher overall mortality and

cancer-specific mortality for recipients with pretransplant history of malignancy; de novo malignancies being the major cause.<sup>48</sup> Unfortunately, pediatric data were not analyzed separately. Undoubtedly, careful long-term follow-up of childhood cancer survivors on KRT regarding secondary malignancies is warranted.

The size of our study population, being one of the largest populations of childhood cancer survivors treated on KRT so far, is definitely a strength of our study. However, several limitations need to be acknowledged. Firstly, this is a registry-based study, and because the ESPN/ERA Registry is a KRT registry, information about (timing of) cancer diagnoses, its consecutive treatment, and cancer remission is limited. As such, we assumed group 2 patients not experiencing renal metastasis of their primary tumor, but we cannot be completely sure. However, the data were complemented using a questionnaire sent to all reporting countries with a response rate of 53%. Secondly, our patient categorization was slightly different compared to previous studies.<sup>14,18,19</sup> We categorized all WT patients into group 1, although definite knowledge about the reason for KRT remained uncertain. This may have affected the outcome results of the groups, but not the findings of KRT-treated cancer survivors in general. Thirdly, data on the KT listing (intention to treat) were unavailable. A small number of cancer survivors in group 1, their controls, and group 2 remained on dialysis at 10 years of

follow-up, but it is unknown whether they were eligible and listed for KT. For that reason, conclusions about access can hardly be drawn. Also, as data collection within the ESPN/ERA Registry on several clinical variables is on a voluntary basis, data on some important parameters, including ethnicity, immunosuppressive protocols, posttransplant lymphoproliferative disease, and growth hormone therapy are lacking (for a subset of patients) and our analyses could not be adjusted for these parameters. Finally, we accept that conclusions from the present study may not be generalized to all cancer patients requiring KRT, as those with poor prognosis were most likely excluded from KT.

In summary, despite childhood cancer survivors' increased mortality when on KRT, the long-term outcome after KT is comparable to matched control subjects. Recognizing this, if eligible, it is beneficial to consider KT in these children early enough in order to reduce their cardiovascular risk and enhance their growth potential. Early multidisciplinary interventions, close monitoring for cancer recurrence and second cancers, and attentive KRT care are essential to optimize the outcomes and quality of life for childhood cancer survivors on KRT.

## Acknowledgments

The authors would like to thank the patients, their parents, and the staff of all the dialysis and transplant units who have contributed data via their national registries and contact persons. The authors also would like to thank R. Topaloglu, J. Oh, and A. Ortiz for being members of the ESPN/ERA Registry Committee, D. Shtiza, F. Engler, J. Kerschbaum, G. Mayer, R. Kramar, O. Raikevic-Liachovskaya, A. Duderavich, I. Sheuchuk, K. van Hoeck and the Centre contributors to the Belgian Registry Committee, D. Pokrajac, D. Roussinov, D. Milosevic, M. Ban, J. Slavicek, D. Arapovic, S. Abdovic, A. Elia, T. Seeman, K. Vondrak, K. Hommel, Ü. Toots, J. Helve, P. Finne, P.-H. Groop, C. Couchoud, M. Lassalle, E. Berard, T. Davitaia, K. Krupka, B. Höcker, L. Pape, B. Tönshoff, K. Rascher, E. Nüsken, L. Weber, G. von Gersdorff, Jörg Dötsch, F. Schaefer, G. Moustakas, A. Kapogiannis, A. Mitsioni, N. Printza, Cs. Berecki, A. Szabó, T. Szabó, A. Barczy, O. Lakatos, A. Végh, R. Palsson, V. Edvardsson, A. Awan, A. K. Heggenstaller, C. Sweeney, N. Dolan, B. Gianoglio, C. Corrado, I. Guzzo, F. Paglialonga, C. Pecoraro, E. Verrina, A. Popova, V. Kuzema, A. Jankauskiene, S. Rudaitis, V. Said-Conti, S. Gatcan, O. Berbeca, N. Zaikova, N. Revenco, S. Pavićević, E. Sahpazova, N. Abazi, A. Åsberg, A. V. Reisæter, A. Bjerre, A. Zurowska, I. Zagozdzon, C. Mota, R. Stone, G. Mircescu, L. Garneata, E. A. Molchanova, E. V. Zakharova, A. M. Andrusev, M. Kostić, B. Spasojević, M. Cvetković, I. Gojković, D. Paripović, G. Miloševski-Lomić, L. Podracka, G. Kolvek, N. Battelino, G. Novljan, J. Buturovic-Ponikvar, A. Alonso-Melgar and the Spanish Paediatric Registry, K. G. Prütz, M. Stendahl, M. Evans, S. Schön, M. Segelmark, T. Lundgren, E. Maurer, G. F. Laube, C. E. Kuehni, P. Parvex, S. Tschumi, L. Mader, L. Heuveling, S. Volgelaar on behalf of the Nefrovisie foundation, D. D. Ivanov, S. P. Fomina, W. Magadi, and S. Marks for contributing data to the ESPN/ERA Registry.

This article was written by H. Kaijansinkko and M. Bonthuis et al on behalf of the ESPN/ERA Registry and the ERA Registry which is an official body of the ERA (European Renal Association).

## Funding

Henna Kaijansinkko has received funding from The Foundation for Pediatric Research, Finland to perform the study. The ESPN/ERA Registry is funded by the ESPN and ERA.

## Author contributions

H.K., M.B., K.J., and T.J. participated in the research design. H.K., M.B., and T.J. participated in the writing of the manuscript. M.B. participated in data analysis. K.J., J.H., E.V., S.A.B., C.I., M.D.S., and K.J.J. participated in the interpretation of the data and revision of the manuscript. R.M.R., C.E.K., E.B., T.K., C.M., B.A., M.S., B.B., B.H., S.F., A.C.G., K.V., H.A., L.A.P., K.H., M.S.M., H.H., and A.A.M. collected patient data, reviewed and edited the manuscript.

## Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

## Data availability

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

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajt.2024.11.002>.

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