Mortality risk in European children with end-stage renal disease on dialysis

Nicholas C. Chesnaye[1], Franz Schaefer[2], Jaap W. Groothoff[3], Marjolein Bonthuis[1], György Reusz[4], James G. Heaf[5], Malcolm Lewis[6], Elisabeth Maurer[7], Dušan Paripović[8], Ilona Zagozdzon[9], Karlijn J. van Stralen[1] and Kitty J. Jager[1]

[1]*ESPN/ERA-EDTA Registry and ERA-EDTA Registry, Amsterdam, the Netherlands;* [2]*Division of Pediatric Nephrology, University of Heidelberg, Center for Pediatrics and Adolescent Medicine, Heidelberg, Germany;* [3]*Department of Pediatric Nephrology, Emma Children's Hospital AMC, Amsterdam, the Netherlands;* [4]*Department of Pediatrics, Semmelweis University, Budapest, Hungary;* [5]*Department of Nephrology, University of Copenhagen, Herlev, Denmark;* [6]*Manchester Children's Hospital, Manchester, United Kingdom;* [7]*University of Bern, Institute of Social and Preventive Medicine, Bern, Switzerland;* [8]*Faculty of Medicine, University of Belgrade, Department of Nephrology, University Children's Hospital, Belgrade, Serbia; and* [9]*Department Pediatrics, Nephrology, and Hypertension, Medical University of Gdansk, Gdansk, Poland*

We aimed to describe survival in European pediatric dialysis patients and compare the differential mortality risk between patients starting on hemodialysis (HD) and peritoneal dialysis (PD). Data for 6473 patients under 19 years of age or younger were extracted from the European Society of Pediatric Nephrology, the European Renal Association, and European Dialysis and Transplant Association Registry for 36 countries for the years 2000 through 2013. Hazard ratios (HRs) were adjusted for age at start of dialysis, sex, primary renal disease, and country. A secondary analysis was performed on a propensity score–matched (PSM) cohort. The overall 5–year survival rate in European children starting on dialysis was 89.5% (95% confidence interval [CI] 87.7%–91.0%). The mortality rate was 28.0 deaths per 1000 patient years overall. This was highest (36.0/1000) during the first year of dialysis and in the 0- to 5-year age group (49.4/1000). Cardiovascular events (18.3%) and infections (17.0%) were the main causes of death. Children selected to start on HD had an increased mortality risk compared with those on PD (adjusted HR 1.39, 95% CI 1.06–1.82, PSM HR 1.46, 95% CI 1.06–2.00), especially during the first year of dialysis (HD/PD adjusted HR 1.70, 95% CI 1.22–2.38, PSM HR 1.79, 95% CI 1.20–2.66), when starting at older than 5 years of age (HD/PD: adjusted HR 1.58, 95% CI 1.03–2.43, PSM HR 1.87, 95% CI 1.17–2.98) and when children have been seen by a nephrologist for only a short time before starting dialysis (HD/PD adjusted HR 6.55, 95% CI 2.35–18.28, PSM HR 2.93, 95% CI 1.04–8.23). Because unmeasured case-mix differences and selection bias may explain the higher mortality risk in the HD population, these results should be interpreted with caution.

Correspondence: *Marjolein Bonthuis, ESPN/ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, University of Amsterdam, PO Box 22700, Amsterdam 1100 DE, the Netherlands. E-mail: m.bonthuis@amc.uva.nl*

Received 2 July 2015; revised 20 January 2016; accepted 11 February 2016

Kidney International (2016) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2016.02.016

KEYWORDS: dialysis modality; end-stage renal disease; mortality risk factors; pediatric nephrology

End-stage renal disease (ESRD) in children is a rare and severe condition, which requires renal replacement therapy (RRT) to sustain life. Renal transplantation is the preferred treatment modality in terms of outcomes, yet most patients will start RRT on dialysis to bridge the preparation time needed for transplantation. Although survival in these children has increased substantially over the past decades, mortality is still ~55 times higher than in the general pediatric population and occurs predominantly in the dialysis population.[1]

Several factors have been shown to affect the mortality risk in the pediatric RRT population, the most influential being age at RRT initiation, transplantation, time on RRT, primary renal disease (PRD), and the presence of comorbidities.[2,3] The few studies that explored the effect of initial dialysis modality on mortality risk in children show conflicting results.[3–5] In Europe, no such study has previously been undertaken on an international scale, and the rarity of pediatric ESRD has limited exploration of the heterogeneity of treatment effect across patient subgroups and time-dependent treatment effects, as has been demonstrated in the adult population.[6–11]

The current study therefore aims to (i) describe survival in European pediatric dialysis patients, (ii) compare the mortality risk in patients starting RRT on HD and PD, and (iii) explore the differential mortality risk in the dialysis population by examining treatment subgroup interactions by sex, PRD, age at the start of RRT, comorbidity presence at the start of RRT, and the time under treatment by a nephrologist before dialysis as a marker for timely referral and the speed of disease progression.

RESULTS

Patient characteristics

Between January 1, 2000, and December 31, 2013, we identified 6473 children younger than 19 years of age starting RRT on dialysis in Europe. Of these patients, 30.9% started at 0 to 5 years of age and 69.1% at 6 to 18 years of age; 56.1% were boys, and 47.8% started dialysis on HD. Most ESRD was caused by congenital anomalies of the kidney and urinary tract (32.4%), followed by glomerulopathies (18.3%), cystic kidney diseases (9.3%), and hereditary nephropathies (7.3%). Of the group of miscellaneous PRDs (8.9%), kidney tumors (1.0%) and unspecified interstitial nephritis (1.0%) were the most common. The number of patients recovering renal function was low for patients starting on HD (N = 51, 0.8%) and PD (N = 33, 0.5%). The number lost to follow-up due to transfer to an adult center was higher in patients starting on HD (N = 328, 5.1%) compared with patients starting on PD (N = 137, 2.1%), reflecting the older HD population transitioning sooner to adult centers. Patient characteristics by initial dialysis modality are provided in Table 1.

Overall mortality in patients on dialysis

A total of 306 deaths occurred during 10,910 patient years (py), equivalent to a mortality rate of 28.0 deaths per 1000 py during the first 5 years of dialysis treatment, while censoring for transplantation. Overall survival rates at 1, 2, and 5 years were 96.6% (95% confidence interval [CI] 96.0%–97.0%), 94.5% (95% CI 93.8%–95.2%), and 89.5% (95% CI 87.7%–91.0%), respectively. Mortality was highest during the first year of dialysis (189 deaths, 36.0 deaths per 1000 py) and in the youngest patients (ages 0–5 years, 189 deaths, 49.4 deaths per 1000 py) and decreased progressively with time on dialysis and with age at dialysis initiation.

Causes of death

Cardiovascular mortality (18.3%) and infection (17.0%) were the main known causes of death, followed by cerebrovascular accidents (7.5%), withdrawal (4.9%), and malignancies (5.2%). Cause of death was missing in 26.1% of cases (21.4% in HD, 29.7% in PD). In the group of cardiovascular deaths, the most common cause was cardiac arrest/sudden death (54.4%), followed by fluid overload/pulmonary edema (16.1%). In the group of infection-related deaths, sepsis was the most common cause of death (61.5%), followed by pulmonary infections (13.5%). Of the miscellaneous causes of death, the most common cause was hemorrhage (due to surgery or other cause, 9.8%), followed by pulmonary embolus (8.2%). The cause of death varied by current treatment modality (Supplementary Figure S1), with cardiovascular mortality (20.5%) as the predominant cause of death in HD patients, whereas infection was the main cause of death in PD patients (19.5%). The cause of death did not differ between the first year on dialysis and the years thereafter. In a sensitivity analysis excluding 4 countries with a high

Table 1 | Patient characteristics by initial dialysis modality

	Ages 0–5 years			Age 6–18 years			PSM ages 0–5 years			PSM age 6–18 years		
	HD (500)	PD (1498)	*P* value	HD (2591)	PD (1884)	*P* value	HD (458)	PD (458)	*P* value	HD (1434)	PD (1434)	*P* value
Sex												
Male	302 (60.4%)	934 (62.4%)	0.44	1411 (54.5%)	987 (52.4%)	0.17	278 (60.7%)	277 (60.5%)	0.95	766 (53.4%)	765 (53.4%)	0.97
Primary renal disease												
CAKUT	116 (23.2%)	582 (38.9%)	<0.0001	780 (34.6%)	621 (33.0%)	<0.0001	114 (24.9%)	128 (28.0%)	0.94	466 (32.5%)	468 (32.6%)	0.99
Glomerulonephritis	81 (16.2%)	185 (12.4%)		555 (21.4%)	365 (19.4%)		70 (15.3)	67 (14.6%)		284 (19.8%)	281 (19.6%)	
Cystic	42 (8.4%)	132 (8.8%)		204 (7.9%)	223 (11.8%)		41 (9.0%)	42 (9.2%)		147 (10.3%)	149 (10.4%)	
Hereditary	51 (10.2%)	152 (10.2%)		170 (6.6%)	98 (5.2%)		45 (9.8%)	42 (9.2%)		79 (5.5%)	79 (5.5%)	
Ischemic	18 (3.6%)	47 (3.1%)		31 (1.2%)	18 (1.0%)		18 (3.9%)	13 (2.8%)		14 (1.0%)	16 (1.1%)	
HUS	34 (6.8%)	87 (5.8%)		84 (3.2%)	63 (3.3%)		31 (6.8%)	37 (8.1%)		45 (3.1%)	49 (3.4%)	
Metabolic	22 (4.4%)	31 (2.1%)		63 (2.4%)	47 (2.5%)		18 (3.9%)	14 (3.1%)		42 (2.9%)	37 (2.6%)	
Vasculitis	3 (0.6%)	1 (0.1%)		102 (3.9%)	45 (2.4%)		2 (0.4%)	1 (0.2%)		44 (3.1%)	42 (2.9%)	
Miscellaneous	75 (15.0%)	147 (9.8%)		237 (9.2%)	117 (6.2%)		64 (14.0%)	58 (12.7%)		99 (6.9%)	102 (7.1%)	
Unknown	58 (11.6%)	134 (9.0%)		365 (14.1%)	287 (15.2%)		55 (12.0%)	56 (12.2%)		214 (14.9%)	211 (14.7%)	
Comorbidity at RRT start[a]												
At least 1	31 (47.2%)	190 (40.3%)	0.86	227 (38.4%)	221 (38.0%)	0.90	28 (36.8%)	30 (48.4%)	0.17	166 (37.3%)	164 (37.7%)	0.90
Time under treatment of a nephrologist[b]												
1–5 months	33 (22.3%)	115 (27.5%)	0.21	69 (13.0%)	70 (12.0%)	0.61	33 (23.6%)	37 (24.0%)	0.93	54 (12.6%)	44 (10.8%)	0.42

CAKUT, congenital anomalies of the kidney and urinary tract; HD, hemodialysis; HUS, hemolytic-uremic syndrome; PD, peritoneal dialysis; PSM, propensity score matched; RRT, renal replacement therapy.
[a]Available for 1725 patients and for 1018 patients in the PSM dataset.
[b]Available for 1681 patients and for 1129 patients in the PSM cohort.