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Mortality Risk Among Children Initially Treated With Dialysis for End-Stage Kidney Disease, 1990-2010

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Importance Most children with end-stage kidney disease (ESKD) are treated with dialysis prior to transplant. It is not known whether their outcomes have changed in recent years.

Objective To determine if all-cause, cardiovascular, and infection-related mortality rates for children and adolescents beginning dialysis improved between 1990 and 2010.

Design, Setting, and Participants Retrospective cohort study of patients younger than 21 years initially treated with dialysis for ESKD, recorded in the United States Renal Data System between 1990 and 2010. Children with a prior kidney transplant were excluded. We used Cox proportional hazard models to estimate the hazard ratios (HRs) for mortality associated with a 5-year increment in year of ESKD treatment initiation. Primary analyses censored observation at kidney transplant.

Main Outcomes and Measures All-cause, cardiovascular, and infection-related mortality.

Results A total of 23 401 children and adolescents who initiated ESKD treatment with dialysis at younger than 21 years between 1990 and 2010 were identified. Crude mortality rates during dialysis treatment were higher among children younger than 5 years at the start of dialysis compared with those who were 5 years and older. Mortality rates for both children and adolescents being treated for ESKD with dialysis decreased significantly between 1990 and 2010.

	1990-1994	1995-1999	2000-2004	2005-2010	Overall (1990-2010)
Age <5 y at ESKD Treatment Initiation					
Total No. of patients	692	734	845	1179	3450
Person-years, No.	1613	1550	1670	2303	7136
All-cause deaths, No.	181	151	181	192	705
Mortality per 1000 person-years	112.2	97.4	108.4	83.4	98.8
Adjusted HR (95% CI) per 5-y increment in calendar year of ESKD initiation, 1990-2010					0.80 (0.75-0.85)
Age ≥5 y at ESKD Treatment Initiation					
Total No. of patients	4368	4661	5103	5819	19 951
Person-years, No.	14 595	15 749	15 350	13 104	58 799
All-cause deaths, No.	651	661	618	340	2270
Mortality per 1000 person-years	44.6	42.0	40.3	25.9	38.6
Adjusted HR (95% CI) per 5-y increment in calendar year of ESKD initiation, 1990-2010					0.88 (0.85-0.92)

Conclusions and Relevance In the United States, there was a substantial decrease in mortality rates over time among children and adolescents initiating ESKD treatment with dialysis between 1990 and 2010. Further research is needed to determine the specific factors responsible for this decrease.

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INDIVIDUALS WITH END-STAGE KIDney disease (ESKD) face a significantly shortened life expectancy.[1] In no group of ESKD patients is the loss of potential years of life larger than in children and adolescents.[2-4] Although transplant remains the treatment of choice to maximize survival, growth, and development, 75% of children with ESKD require treatment with dialysis prior to receiving a kidney transplant.[1,5] Dialysis is therefore a lifesaving therapy for children with ESKD while they await transplant. Nevertheless, all-cause mortality rates in children receiving maintenance dialysis are at least 30 times higher than the general pediatric population, with even higher relative risks in very young children.[2] The 2 most common causes of death in children with ESKD are cardiovascular disease and infection.[2-4,6,7] There have been substantial improvements in the care of children with ESKD between 1990 and 2010. However, to our knowledge, it is not known if mortality has changed over time in the United States, particularly in recent years.[2,6,7]

The objective of this study was to determine if all-cause, cardiovascular, and infection-related mortality rates have changed between 1990 and 2010 among children and adolescents with ESKD initially treated with dialysis and if changes in mortality rates over time differed by age at treatment initiation. Based on a study in the Australian and New Zealand pediatric ESKD popula-

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tion[2] and on the greater potential for improvement in younger children, we hypothesized that mortality rates have improved in the United States between 1990 and 2010 and that improvements have been greater for younger compared with older children.

METHODS

Data Source and Population

This was a retrospective cohort study of individuals recorded in the United States Renal Data System (USRDS) database who initiated ESKD treatment with dialysis for the first time at younger than 21 years of age between January 1, 1990, and December 31, 2010, and who were followed up until December 31, 2010. The USRDS includes virtually all children treated for ESKD in the United States (eMethods, available at http://www.jama.com).[1,8] Because a comprehensive version of the death notification form came into use January 1, 1990, we chose this as the start date.[1,4] Patients with a prior kidney transplant were excluded, as were patients receiving preemptive transplant. We divided the observation interval into 4 approximately equal periods to highlight how patient characteristics, cause of death, and the amount of missing data have changed over time.[1,8] The institutional review board at The Children's Hospital of Philadelphia approved the study.

Primary Exposure and Outcome Variables

The primary exposure was the calendar year of ESKD treatment initiation. The primary outcome was all-cause mortality. Cardiovascular and infection-related mortality were also considered as outcomes. Cause of death was determined from the USRDS death notification form (eMethods, TABLE 1). Deaths are reported to the USRDS via several different mechanisms, ensuring virtually complete capture.[1]

Association Between Year of Initiation and Mortality Rate

We calculated mortality rates (deaths per 1000 person-years of observation) for each year of initiation and plotted the data to characterize the "shape" of the relationship. Although there was year-to-year variability in mortality, overall mortality rates decreased gradually and linearly with year of initiation; there were no clear "step" changes. Therefore, initiation year was treated as a continuous variable.

We generated Kaplan-Meier curves to illustrate differences in mortality among 4 approximately equal time periods within the 1990-2010 interval. We used Cox proportional hazards models to estimate the relative mortality (hazard ratios [HRs] and 95% CIs) associated with a 5-year increment in calendar year of ESKD treatment initiation from 1990-2010. Because we were interested in examining changes in mortality over calendar time during treatment with dialysis, observation was limited to the period of dialysis prior to a first transplant. Time zero was the day of dialysis initiation, and observation was censored at first transplant, death, or end of observation. We considered the possibility of different relationships between year of initiation and mortality in different age groups by including multiplicative year × age interaction terms in the models. Based on prior studies[2,4,6] and the age categories used in the USRDS annual reports,[1] age at initiation was divided into 2 categories (<5 years and ≥5 years). Proportionality of hazards was confirmed by examining plots of the data.

Although virtually all children treated for ESKD are considered eligible for transplantation, and therefore a problem with competing risks is unlikely, we performed sensitivity analyses in which the person-time of patients who were not censored because of transplant was weighted by the inverse of their probability of continuing to receive dialysis.[9] The weights were determined by fitting a logistic regression model to estimate the probability of being censored because of transplant, given a particular profile of all the other covariates in the models. Such weighting creates a pseudo population without transplant censoring such that the weighted population is no longer a biased sample. In addition, we conducted analyses in which observation was not censored at transplant; these analyses include observation during treatment with dialysis as well as with transplant.

Models were initially adjusted for age at dialysis initiation (as a continuous variable within each stratum), sex, race, socioeconomic status (SES), primary kidney disease, and initial dialysis modality. Socioeconomic status was estimated using median household income by zip code and classified by quartile within the US Census data (1999).[10] Subsequent models were also adjusted for insurance coverage and comorbidity; these variables were associated with relatively greater amounts of missing data, especially in earlier time periods, so were added sequentially to the models. In addition, reporting of both insurance coverage and comorbidity has changed over time (eTable 1). Estimated glomerular filtration rate (eGFR; estimated from height and serum creatinine level within 3 months of dialysis initiation using the updated Schwartz formula[11]) and erythrocyte-stimulating agent (ESA) use at initiation were examined but were not included in the multivariable analyses because of very large amounts of missing data.

Imputation of Missing Covariates and Missing Cause of Death

For the all-cause mortality models, missing covariate values were imputed using multiple imputation methods[12] and the joint distributions of all other variables in the models, including outcomes (eMethods). Similarly, for cardiovascular and infection-related mortality models, missing causes of death and missing covariates were imputed from the joint distributions of all other variables in the models, including nonmissing causes of death.[12] We also report analyses including only cases with nonmissing cause of death.

Data analyses were performed using SAS version 9.2 (SAS Institute) and

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Table 1. Patient Characteristics by Year of Treatment Initiation for End-Stage Kidney Disease

	Age <5 y at ESKD Treatment Initiation				Age ≥5 y at ESKD Treatment Initiation			
	1990-1994	1995-1999	2000-2004	2005-2010	1990-1994	1995-1999	2000-2004	2005-2010
No. of patients	692	734	845	1179	4368	4661	5103	5819
Age at first ESKD care, median (IQR), y								
All patients	1.0 (0.2-2.6)	1.1 (0.2-2.6)	0.9 (0.1-2.4)	0.6 (0.1-2.0)	17.1 (13.5-19.3)	17.0 (13.4-19.3)	16.8 (13.3-19.3)	17.1 (14.0-19.4)
Initiating hemodialysis	1.2 (0.4-3.2)	1.6 (0.5-3.1)	1.7 (0.3-3.5)	0.5 (0.1-2.4)	18.0 (15.3-19.7)	18.0 (15.2-19.7)	17.9 (14.8-19.7)	18.0 (15.3-19.8)
Initiating peritoneal dialysis	0.8 (0.2-2.3)	0.8 (0.1-2.4)	0.7 (0.1-2.0)	0.6 (0.1-1.9)	15.0 (11.4-18.1)	14.6 (11.2-17.6)	14.1 (10.8-17.1)	14.6 (11.1-17.1)
Male sex, No. (%)	432 (62.4)	447 (60.9)	522 (61.8)	762 (64.6)	2360 (54.0)	2503 (53.7)	2733 (53.6)	3163 (54.4)
Race, No. (%)								
White	538 (77.8)	541 (73.7)	604 (71.5)	858 (72.8)	2720 (62.3)	2776 (59.6)	3043 (59.6)	3830 (65.8)
Black	122 (17.6)	136 (18.5)	145 (17.2)	183 (15.5)	1342 (30.7)	1523 (32.7)	1533 (30.0)	1473 (25.3)
Other	32 (4.6)	57 (7.8)	96 (11.4)	138 (11.7)	306 (7.0)	362 (7.8)	527 (10.3)	516 (8.9)
Primary kidney disease, No. (%)[a]								
CAKUT	194 (28.0)	286 (39.0)	347 (41.1)	447 (37.8)	461 (10.6)	815 (17.5)	887 (17.4)	1043 (17.9)
Glomerulonephritis	83 (12.0)	42 (5.7)	27 (3.2)	35 (3.0)	1557 (35.6)	1627 (34.8)	1655 (32.4)	1723 (29.6)
FSGS	29 (4.2)	44 (6.0)	42 (5.0)	59 (5.0)	467 (10.7)	669 (14.4)	800 (15.7)	866 (14.9)
Other	210 (30.3)	311 (42.4)	370 (43.7)	497 (42.2)	778 (17.8)	811 (17.4)	888 (17.4)	1046 (18.0)
Unknown	37 (5.4)	23 (3.1)	53 (6.3)	88 (7.5)	556 (12.7)	638 (13.7)	826 (16.2)	1025 (17.6)
Missing	139 (20.1)	28 (3.8)	6 (0.7)	53 (4.5)	549 (12.6)	101 (2.2)	47 (0.9)	116 (2.0)
Modality initiated, No. (%)								
Hemodialysis	133 (19.2)	142 (19.3)	164 (19.4)	290 (24.6)	2540 (58.2)	2898 (62.2)	3358 (65.8)	3869 (66.5)
Peritoneal dialysis	497 (71.8)	538 (73.3)	633 (74.9)	793 (67.3)	1567 (35.9)	1586 (34.0)	1511 (29.6)	1555 (26.7)
Missing	62 (9.0)	54 (7.4)	48 (5.7)	96 (8.1)	261 (6.0)	177 (3.8)	234 (4.6)	395 (6.8)
Socioeconomic quartile, No. (%)[a]								
Lowest	137 (19.8)	175 (23.8)	169 (20.0)	197 (16.7)	1118 (25.6)	1136 (24.4)	1253 (24.6)	1378 (23.7)
Mid-low	133 (19.2)	121 (16.5)	159 (18.8)	209 (17.7)	798 (18.3)	936 (20.1)	959 (18.8)	1150 (19.8)
Mid-high	167 (24.1)	156 (21.3)	194 (23.0)	276 (23.4)	1074 (24.6)	1097 (23.5)	1216 (23.8)	1348 (23.2)
Highest	231 (33.4)	249 (33.9)	298 (35.3)	401 (34.0)	1171 (26.8)	1272 (27.3)	1454 (28.5)	1655 (28.4)
Missing	24 (3.5)	33 (4.5)	25 (3.0)	96 (8.1)	207 (4.7)	220 (4.7)	221 (4.3)	288 (5.0)
Comorbidities, No. (%)[a]								
None	210 (30.4)	601 (81.9)	711 (84.1)	757 (64.2)	1582 (36.2)	3876 (83.2)	4441 (87.0)	4641 (79.8)
≥1 Comorbidity	27 (3.9)	101 (13.8)	126 (14.9)	367 (31.1)	361 (8.3)	655 (14.1)	611 (12.0)	1052 (18.1)
Missing	455 (65.8)	32 (4.4)	8 (1.0)	55 (4.7)	2425 (55.5)	130 (2.8)	51 (1.0)	126 (2.2)
Insurer, No. (%)[a]								
Public	108 (15.6)	267 (36.4)	368 (43.6)	567 (48.1)	1024 (23.4)	1509 (32.4)	1809 (35.5)	2382 (40.9)
Private	114 (16.5)	367 (50.0)	440 (52.1)	533 (45.2)	743 (17.0)	2217 (47.6)	2553 (50.0)	2607 (44.8)
No coverage	11 (1.6)	35 (4.8)	28 (3.3)	17 (1.4)	128 (2.9)	611 (13.1)	683 (13.4)	698 (12.0)
Missing	459 (66.3)	65 (8.9)	9 (1.1)	62 (5.3)	2473 (56.6)	324 (7.0)	58 (1.1)	132 (2.3)
eGFR, mL/min/1.73 m^2 at initiation, median (IQR)[a]	8.3 (6.2-11.4)	7.3 (5.5-10.3)	8.5 (6.2-12.0)	9.8 (6.8-14.3)	7.9 (5.8-10.7)	6.6 (4.9-8.6)	7.4 (5.4-9.8)	8.2 (5.8-11.2)
Missing, %	71.8	43.1	36.0	36.6	62.8	12.7	3.6	4.4
Erythrocyte-stimulating agent use at initiation, No. (%)[a]	122 (17.6)	277 (37.7)	333 (39.4)	468 (39.7)	731 (16.7)	1330 (28.5)	1772 (34.7)	1857 (31.9)
Missing, No. (%)	492 (71.1)	91 (12.4)	10 (1.2)	55 (4.7)	2689 (61.6)	456 (9.8)	54 (1.1)	126 (2.2)
Dialysis time before first transplant, median (IQR), y	1.3 (0.6-2.7)	1.4 (0.7-2.6)	1.5 (0.9-2.4)	1.3 (0.7-2.1)	1.3 (0.5-2.9)	1.4 (0.6-3.0)	1.5 (0.7-2.8)	0.9 (0.5-1.6)
No. of transplants before end of observation	486	550	612	490	3467	3580	3668	2637
Cause of death during treatment with dialysis, No. (%)[b]								
Cardiovascular	57 (31.5)	46 (30.5)	57 (31.5)	52 (27.1)	236 (36.3)	260 (39.3)	234 (37.9)	122 (35.9)
Infection	25 (13.8)	34 (22.5)	40 (22.1)	37 (19.3)	104 (16.0)	123 (18.6)	95 (15.4)	33 (9.7)
Malignancy	7 (3.9)	9 (6.0)	4 (2.2)	7 (3.7)	10 (1.5)	8 (1.2)	14 (2.3)	15 (4.4)
Hemorrhage	2 (1.1)	5 (3.3)	4 (2.2)	2 (1.0)	15 (2.3)	24 (3.6)	25 (4.0)	3 (0.9)
Metabolic	0	1 (0.7)	2 (1.1)	1 (0.5)	18 (2.8)	22 (3.3)	8 (1.3)	7 (2.1)
Other	9 (5.0)	9 (6.0)	11 (6.1)	22 (11.5)	39 (6.0)	47 (7.1)	61 (9.9)	38 (11.2)
Unknown	24 (13.3)	26 (17.2)	35 (19.3)	17 (8.9)	87 (13.4)	87 (13.2)	65 (10.5)	27 (7.9)
Missing	57 (31.5)	21 (13.9)	28 (15.5)	54 (28.1)	142 (21.8)	90 (13.6)	116 (18.8)	95 (27.9)

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; IQR, interquartile range.

[a] The changes in reporting of comorbidity, laboratory values, cause of death, medication use, and insurance status over time are shown in eTable 1.

[b] Deaths were classified as cardiovascular if the cause of death was recorded as any of the following: acute myocardial infarction, pericarditis, cardiac tamponade, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest (cause unknown), valvular heart disease, congestive heart failure, pulmonary embolus, or cerebrovascular accident including intracranial hemorrhage. Infection-related causes included septicemia, peritoneal access infection, peritonitis, viral hepatitis, viral infection, tuberculosis, AIDS, or infections of the central nervous system, heart, lungs, abdomen, and genitourinary systems.

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Table 2. Crude All-Cause Mortality Rates and All-Cause Hazard Ratios for Mortality, Stratified by Age

	Age <5 y at ESKD Treatment Initiation	Age ≥5 y at ESKD Treatment Initiation
1990-1994		
Person-years of observation	1613	14 595
Deaths, No.	181	651
Crude all-cause mortality rate per 1000 person-years	112.2	44.6
1995-1999		
Person-years of observation	1550	15 749
Deaths, No.	151	661
Crude all-cause mortality rate per 1000 person-years	97.4	42.0
2000-2004		
Person-years of observation	1670	15 350
Deaths, No.	181	618
Crude all-cause mortality rate per 1000 person-years	108.4	40.3
2005-2010		
Person-years of observation	2303	13 104
Deaths, No.	192	340
Crude all-cause mortality rate per 1000 person-years	83.4	25.9
Entire interval: 1990-2010		
Person-years of observation	7136	58 799
Deaths, No.	705	2270
Crude all-cause mortality rate per 1000 person-years	98.8	38.6
HR per 5-y increment in calendar year of ESKD treatment initiation (95% CI)		
Unadjusted	0.84 (0.78-0.89)	0.87 (0.83-0.90)
Adjusted model 1[a]	0.82 (0.77-0.87)	0.88 (0.85-0.92)
Adjusted model 2 (model 1 plus insurance coverage)	0.82 (0.77-0.87)	0.89 (0.86-0.93)
Adjusted model 3 (model 2 plus comorbidity)	0.80 (0.75-0.85)	0.88 (0.85-0.92)

Abbreviations: ESKD, end-stage kidney disease; HR, hazard ratio.
[a]Model 1 adjusted for age at initiation, sex, race, primary renal disease, initial dialysis modality, and socioeconomic status quartile.

S-plus (version 6.1); a 2-sided P value <.05 was considered statistically significant.

RESULTS

Patient Characteristics and Causes of Death

We identified 23 401 children and adolescents who initiated ESKD treatment with dialysis at younger than 21 years from January 1990 until December 2010. Table 1 summarizes patient characteristics and causes of death by age stratum and over time. Age at ESKD treatment initiation decreased over time among those younger than 5 years. This decrease was more marked among those initiating hemodialysis than peritoneal dialysis. Although most younger children initiated peritoneal dialysis and older patients initiated hemodialysis, there was a slight increase in the use of hemodialysis over time in both age groups.

Comorbidities were uncommon but appeared to increase slightly over time, especially in younger children. Predialysis care, as measured using eGFR and ESA use at initiation, did not appear to change over time. Cardiovascular disease and infection were the most frequently documented causes of death in both age strata and in all time periods. Cardiac arrest (cause unknown) was the most common cardiovascular cause of death in both younger (53%) and older (49%) individuals receiving dialysis.

Change in Mortality Risk Over Time

All-Cause Mortality. Crude mortality rates were higher in children younger than 5 years compared with those 5 years and older at initiation (TABLE 2). Mortality risk decreased progressively over calendar time for both those younger than 5 years and those 5 years and older at initiation. The FIGURE illustrates the survival, during dialysis treatment, of patients initiating ESKD care in 4 calendar time periods between 1990 and 2010 for each age stratum. Each 5-year increment in calendar year of dialysis initiation was associated with an adjusted HR of 0.80 (95% CI, 0.75-0.85) among children younger than 5 years at initiation and an HR of 0.88 (95% CI, 0.85-0.92) among those 5 years and older. The magnitude of this improvement was greater for younger children than older children; however, this difference did not reach statistical significance (interaction P=.10). The sensitivity analyses, including analyses without censoring at transplant and analyses in which inverse probability of censoring weighting was applied, returned qualitatively similar results (eFigure 1, eTable 2).

The multivariable Cox models also permitted identification of factors independently associated with all-cause mortality (TABLE 3). Higher mortality risk was independently associated with glomerulonephritis and "other" primary renal disease (vs congenital anomalies of the kidney or urinary tract), presence of 1 or more comorbidity, and lower estimated SES in both age groups. In children younger than 5 years at initiation, younger age, unknown primary renal disease, and hemodialysis were associated with higher mortality risk. In children 5 years and older at initiation, female sex, black race (vs white), and public insurance (vs no insurance) were associated with higher mortality risk.

Cardiovascular and Infection-Related Mortality. TABLE 4 shows crude cardiovascular and infection-related mortality rates for both age groups as well as the HRs for mortality associated with a 5-year increment in calendar year of ESKD treatment initiation. For cardiovascular mortality, each 5-year increment in calendar year of initiation of dialysis was associated with an adjusted HR of 0.54 (95% CI, 0.47-0.63) among children younger than 5 years at initiation and an HR of 0.66 (95% CI, 0.61-0.70) among those 5

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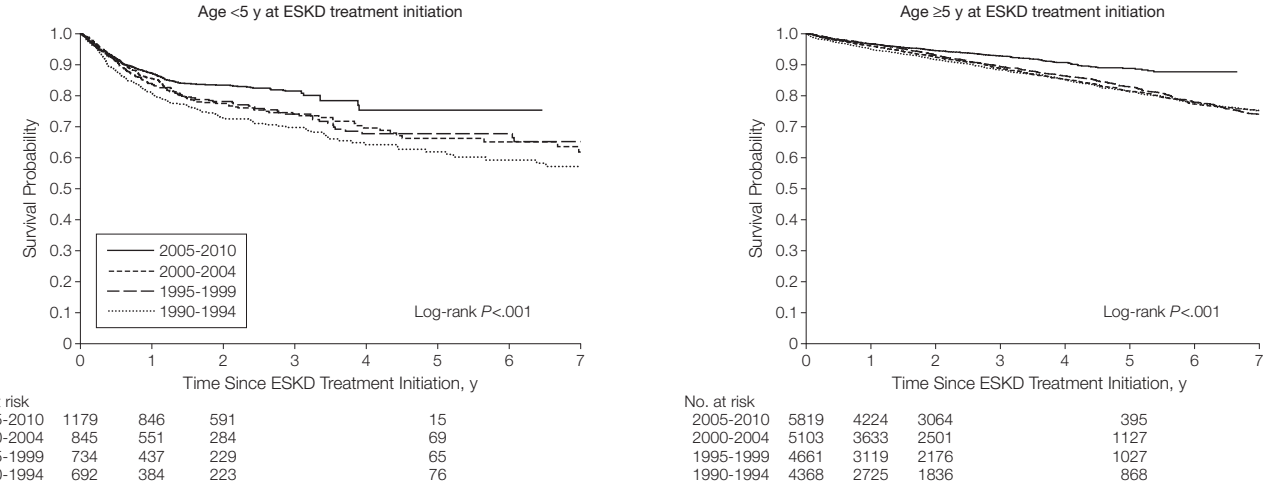
Figure. Kaplan-Meier Estimates of Survival for Children Initiating ESKD Treatment With Dialysis in Successive Time Periods



No. at risk

2005-2010	1179	846	591	15
2000-2004	845	551	284	69
1995-1999	734	437	229	65
1990-1994	692	384	223	76

No. at risk

2005-2010	5819	4224	3064	395
2000-2004	5103	3633	2501	1127
1995-1999	4661	3119	2176	1027
1990-1994	4368	2725	1836	868

Observation was censored at first transplant. The numbers of individuals still under observation, and still treated with dialysis, are indicated below the curves. ESKD indicates end-stage kidney disease.

years and older. For infection-related mortality, each 5-year increment in calendar year of initiation of dialysis was associated with an adjusted HR of 0.64 (95% CI, 0.52-0.79) among children younger than 5 years at initiation and an HR of 0.59 (95% CI, 0.53-0.65) among those 5 years and older. The sensitivity analyses, including analyses without censoring at transplant and analyses including only cases with nonmissing cause of death, were similar (eTable 3).

DISCUSSION

To our knowledge, this study represents the largest cohort of pediatric ESKD patients ever examined, including more than 20 000 individuals who initiated dialysis over the course of 2 decades and were followed up until the end of 2010. We demonstrate that mortality rates for children and adolescents being treated for ESKD with dialysis improved significantly between 1990 and 2010. Although gains in survival appeared slightly greater for children younger than 5 years at initiation of ESKD care, the interaction between age and year of dialysis initiation was not statistically significant.

Our findings expand on the results of prior work. A study of 1634 Australian and New Zealand children (<20 years) initiating treatment for ESKD from 1963-2002 reported significantly lower mortality among those initiating dialysis after 1983 (compared with before 1983) but not after 1993 (compared with earlier years).[2] Although the sample was small, the youngest children appeared to experience the greatest improvements in survival over time. A Dutch study of 381 patients younger than 15 years at ESKD initiation found lower mortality among those starting dialysis after 1982 (vs before 1982).[7] In contrast, no significant changes in all-cause or cardiac mortality were seen between 1991 and 1996 in a USRDS study of 1454 incident dialysis patients (<20 years).[6] These prior studies all identified children younger than 5 to 6 years as having the highest risk for death.[2,6,7]

The association observed between mortality and age in children with ESKD mirrors the association observed in the general pediatric population: mortality risk increases with decreasing age less than 5 years and increases with increasing age beyond about 10 years.[13] However, the causes of death in children with ESKD are very different from those in the general population. Whereas accidents and homicides are the most common causes of death in the general population of children and adolescents,[14,15] cardiovascular disease and infection are the 2 leading causes of death in those with ESKD.[2-4,7,16]

Numerous factors may have contributed to the observed reductions in mortality risk over time. Improved predialysis care, advances in dialysis technology, and greater experience of clinicians may each have played a role.[17-20] We were limited in our ability to examine predialysis care by the information available in this comprehensive US ESKD registry. Large proportions of patients—particularly younger children and those initiating treatment in earlier years—had data missing for ESA use prior to and for eGFR at initiation of dialysis. Therefore, we can only speculate on which specific factors may be responsible for the observed improvements over time in mortality. eFigure 2 highlights advances in dialysis care over time, including regulatory approval of new medications,[21] publication of clinical practice guidelines, and improved technology for performing dialysis.[17,22-25] Although most improvements occurred before 2000, it may take several years to implement new technology and guidelines,[26] and year of implementation likely varies across centers.

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Table 3. Associations Between Covariates and Mortality

	No. of Patients	Person-Years	No. of Deaths	Death Rate per 1000 Person-Years	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Age <5 y at ESKD Treatment Initiation						
Age at initiation (per year)	3450	7136	705	98.8	0.77 (0.73-0.82)	0.75 (0.70-0.80)
Sex						
Female	1287	2655	293	110.4	Reference	Reference
Male	2163	4482	412	91.9	0.83 (0.72-0.97)	0.86 (0.73-1.00)
Race						
White	2541	5036	480	95.3	Reference	Reference
Black	586	1408	150	106.5	1.24 (1.03-1.48)	1.17 (0.96-1.41)
Other	323	692	75	108.4	1.18 (0.93-1.50)	1.22 (0.95-1.41)
Primary disease						
CAKUT	1274	2651	199	75.1	Reference	Reference
Glomerulonephritis	187	300	32	106.7	1.56 (1.13-2.14)	1.49 (1.08-2.04)
FSGS	174	321	12	37.4	0.93 (0.48-1.79)	1.25 (0.78-2.00)
Other	1388	2949	301	102.1	1.42 (1.17-1.71)	1.35 (1.11-1.63)
Unknown	201	390	80	205.1	2.68 (2.01-3.57)	2.06 (1.56-2.73)
Dialysis modality						
Hemodialysis	729	1439	192	133.4	Reference	Reference
Peritoneal dialysis	2461	5408	418	77.3	0.62 (0.52-0.73)	0.71 (0.58-0.85)
SES quartile						
Lowest	678	1497	176	117.6	Reference	Reference
Mid-low	622	1295	133	102.7	0.90 (0.69-1.18)	0.90 (0.71-1.13)
Mid-high	793	1565	148	94.6	0.79 (0.62-1.00)	0.84 (0.67-1.05)
Highest	1179	2392	212	88.6	0.77 (0.61-0.97)	0.79 (0.64-0.98)
Comorbidity						
None	2279	4740	326	68.8	Reference	Reference
≥1	621	1230	189	153.7	1.81 (1.53-2.14)	1.63 (1.10-1.34)
Insurance coverage						
None	91	176	20	113.6	Reference	Reference
Public	1310	2801	257	91.8	0.70 (0.49-1.01)	0.81 (0.53-1.25)
Private	1454	2904	231	79.5	0.60 (0.43-0.85)	0.76 (0.47-1.23)
Age ≥5 y at ESKD Treatment Initiation						
Age at initiation (per year)	19 951	58 799	2270	38.6	1.01 (0.99-1.02)	1.00 (0.99-1.02)
Sex						
Female	9192	27 529	1230	44.7	Reference	Reference
Male	10 759	31 269	1040	33.3	0.74 (0.68-0.81)	0.79 (0.73-0.86)
Race						
White	12 369	30 923	1053	34.1	Reference	Reference
Black	5871	22 249	1021	45.9	1.32 (1.21-1.44)	1.32 (1.21-1.45)
Other	1711	5626	196	34.8	1.07 (0.87-1.19)	1.09 (0.94-1.27)
Primary disease						
CAKUT	3206	7642	198	25.9	Reference	Reference
Glomerulonephritis	6562	20 328	822	40.4	1.48 (1.27-1.72)	1.33 (1.13-1.56)
FSGS	2802	8015	190	23.7	1.01 (0.84-1.22)	0.91 (0.75-1.10)
Other	3523	9236	578	62.6	2.26 (1.93-2.64)	1.92 (1.64-2.25)
Unknown	3045	10 790	290	26.9	1.00 (0.84-1.20)	0.92 (0.76-1.11)
Dialysis modality						
Hemodialysis	12 665	41 308	1566	37.9	Reference	Reference
Peritoneal dialysis	6219	15 937	537	33.7	0.93 (0.84-1.02)	0.96 (0.87-1.07)
SES quartile						
Lowest	4885	16 928	738	43.6	Reference	Reference
Mid-low	3843	11 603	446	38.4	0.91 (0.81-1.02)	0.90 (0.80-1.01)
Mid-high	4735	13 770	504	36.6	0.86 (0.77-0.97)	0.88 (0.78-1.00)
Highest	5552	13 745	471	34.3	0.82 (0.73-0.92)	0.86 (0.75-0.98)
Comorbidity						
None	14 540	39 866	1105	27.7	Reference	Reference
≥1	2679	8051	553	68.7	1.98 (1.78-2.21)	1.84 (1.65-2.07)
Insurance coverage						
None	2120	7660	202	26.4	Reference	Reference
Public	6724	20 466	815	39.8	1.37 (1.17-1.60)	1.25 (1.07-1.46)
Private	8120	18 802	595	31.6	1.12 (0.98-1.29)	1.12 (0.96-1.30)

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; HR, hazard ratio; SES, socioeconomic status.

[a] Adjusted for age at initiation, sex, race, primary renal disease, initial dialysis modality, SES quartile, comorbidity, and insurance status (model 3).

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If there were greater improvements in all-cause mortality rates for younger compared with older children, these may be related to changes specifically targeting small children, including dialysis equipment geared to small body size and age-specific surgical techniques for placing vascular access for dialysis.[17,27,28] It is possible the increasing experience of clinicians treating small children, combined with the implementation of new technologies, may also have played a role.

The broader implementation of clinical practice guidelines[29] may explain some of the improvements in cause-specific mortality. For example, the use of downward-facing, double-cuffed, swan neck peritoneal dialysis catheters increased from 5% (1992-1995) to 24% (after 2002), potentially decreasing the risk of peritonitis, especially in young children.[17] Strict infection control practices may have decreased hemodialysis catheter infections.[30] Pneumococcal and influenza vaccination, which are associated with decreased mortality in adults with ESKD,[31] have been increasingly used over the past decade in children with ESKD.[1] Improvement in anemia care may have contributed to decreased cardiovascular risk. Anemia is associated with a higher risk of death in children initiating dialysis.[32,33] It is therefore worth noting that the mean hemoglobin levels in children with ESKD increased from 9 g/dL in 1991 to more than 11 g/dL in 2007, paralleling an increase in weekly ESA dosing.[1] However, the ideal hemoglobin target for adults treated with ESAs for ESKD has yet to be established, and there have been no trials on the effect of ESA therapy on outcomes in children.

Because time receiving dialysis is so brief in children (median <2 years) compared with adults, it is important to recognize that even the dramatic improvements in mortality risk over time that we observed may not translate into major improvements in overall mortality in children with ESKD. Waiting times for transplant have fallen for older children, primarily since 2005.[34] Therefore, time of exposure to dialysis and its associated higher risk of death compared with transplant[5] have decreased. However, for individuals requiring prolonged treatment with dialysis, including infants who must grow large enough to safely receive transplants, the reductions in mortality risk that have occurred over time may have a notable effect.

The improvements observed in cardiovascular and infection-related mortality rates over time during treatment with dialysis appeared to be larger than the improvements in all-cause mortality. This suggests that mortality from other causes may have increased over calendar time. However, these results must be interpreted with caution. Substantial numbers of patients had data missing for cause of death. Some covariates were also missing in large pro-

Table 4. Cardiovascular and Infection-Related Mortality by Age at Treatment Initiation for End-Stage Kidney Disease

	Cardiovascular Mortality		Infection-Related Mortality	
	Age <5 y	Age ≥5 y	Age <5 y	Age ≥5 y
1990-1994				
Person-years of observation	1613	14 595	1613	14 595
Deaths, No.	57	236	25	104
Crude mortality rate per 1000 person-years	35.3	16.2	15.5	7.1
1995-1999				
Person-years of observation	1550	15 749	1550	15 749
Deaths, No.	46	260	34	123
Crude mortality rate per 1000 person-years	29.7	16.5	21.9	7.8
2000-2004				
Person-years of observation	1670	15 350	1670	15 350
Deaths, No.	57	234	40	95
Crude mortality rate per 1000 person-years	34.1	15.2	24.0	6.2
2005-2010				
Person-years of observation	2303	13 104	2303	13 104
Deaths, No.	52	122	37	33
Crude mortality rate per 1000 person-years	22.6	9.3	16.0	2.5
Entire interval: 1990-2010				
Person-years of observation	7136	58 799	7136	58 799
Deaths, No.	246	852	136	355
Crude mortality rate per 1000 person-years	34.5	14.5	19.1	6.0
HR per 5-y increment in calendar year of ESKD treatment initiation (95% CI)				
Unadjusted	0.80 (0.71-0.90)	0.90 (0.85-0.96)	0.88 (0.75-1.04)	0.82 (0.74-0.90)
Adjusted model 1[a]	0.77 (0.69-0.86)	0.92 (0.86-0.98)	0.84 (0.73-0.96)	0.83 (0.76-0.91)
Adjusted model 2 (model 1 plus insurance coverage)	0.77 (0.67-0.87)	0.92 (0.87-0.98)	0.84 (0.71-0.99)	0.84 (0.76-0.92)
Adjusted model 3 (model 2 plus comorbidity)	0.54 (0.47-0.63)	0.66 (0.61-0.70)	0.64 (0.52-0.79)	0.59 (0.53-0.65)

Abbreviations: ESKD, end-stage kidney disease; HR, hazard ratio.
[a] Adjusted for age at initiation, sex, race, primary renal disease, initial dialysis modality, and socioeconomic status quartile.

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portions, particularly in earlier years. In addition, there were changes over time in reporting of both causes of death and comorbidities. We used multiple imputation to deal with missing covariates and missing causes of death. Although this method is far less likely to introduce bias than including only cases with complete data,[12] it does have limitations, which may be amplified as the proportion of patients with missing data increases. Imputation assumes that one can accurately predict the value of a variable from the other variables in the model. Where both the outcome (cause of death) and covariates are missing in the same patients, predictive capacity may be weak. The marked change in the magnitude of the HRs when comorbidity was included in the models, compared with when it was excluded, suggests either that comorbidity increased substantially over time or, more likely, that the imputation broke down on inclusion of comorbidity.

The HRs associated with some of the covariates included in our models suggest that certain children and adolescents undergoing dialysis may be at a higher risk of death than others. These HRs must be interpreted cautiously; our study was not designed to identify risk factors for death. Furthermore, the wide confidence intervals for some of these estimates suggest that power was limited. Some of the factors we identified, including black race, lower SES, and presence of comorbidity, have previously been shown to be associated with higher mortality risk.[4-6,35] A higher independent risk of death in girls and young women, compared with boys and young men, was observed previously[5] and deserves further investigation. The lower risk of death that we observed in children younger than 5 years initiating peritoneal dialysis, compared with hemodialysis, has also been described by others.[1] It is important to recognize that we could only assess the initial dialysis modality. Up to 20% of pediatric dialysis patients switch modalities, often within the first few months of treatment.[36] Prior analyses in which dialysis modality was treated as a time-dependent variable found higher mortality rates associated with peritoneal dialysis.[2] We observed a higher risk of death in older children with public insurance compared with no insurance. This finding may simply reflect problems imputing insurance status, which was frequently missing in early years.

Our analysis has several strengths, including a large sample size and virtually complete capture of deaths. However, we acknowledge limitations. We cannot exclude the possibility that residual confounding by variables not captured in the USRDS contributed to the associations observed.[37] Changes in the reporting of some variables between 1990 and 2010 may also have limited our ability to completely adjust for all potential confounders. In particular, our ability to completely adjust for insurance coverage and comorbidities was limited by large amounts of missing data in early years. Selection bias may have played a role in the observed improvements in mortality rates over time if physicians tended to not offer dialysis to sicker patients in more recent compared with more remote years. However, the stable or increasing prevalence of comorbidities over time argues against such bias. Our ability to adjust for SES was limited by the measure used to reflect SES: median household income by zip code provides a fairly rough estimate of individual-level SES.

We also acknowledge that cardiovascular mortality rates were strongly influenced by the inclusion of the code "cardiac arrest (cause unknown)." This is a particularly problematic code because it may include arrhythmias due to hyperkalemia, embolic events, or other noncardiac conditions. Including "cardiac arrest (cause unknown)" as a cardiovascular death may result in overestimation of cardiovascular mortality rates. However, prior studies in both the United States and elsewhere reported similar cardiovascular mortality rates in the pediatric dialysis population.[2,7]

Almost all children initiating ESKD treatment are considered eligible for transplant.[2,5] However, most will require dialysis during their lifetime, either before transplant or after allograft loss.[5] In the United States, there was a significant decrease in mortality rates over time among children and adolescents initiating ESKD treatment with dialysis between 1990 and 2010. Further research is needed to determine the specific factors responsible for this decrease.

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