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Authors
Ahearn, Patrick
Johansen, Kirsten L
McCulloch, Charles E
et al.

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Sex Disparities in Risk of Mortality Among Children With ESRD

Patrick Ahearn, MD[*], **Kirsten L. Johansen, MD**[*], **Charles E. McCulloch, PhD**[†], **Barbara A. Grimes, PhD**[†], and **Elaine Ku, MD, MAS**[*,‡]

[*]Division of Nephrology, Department of Medicine, University of California, San Francisco, California

[†]Department of Epidemiology and Biostatistics, University of California, San Francisco, California

[‡]Division of Pediatric Nephrology, Department of Pediatrics, University of California, San Francisco, California

Abstract

Rationale & Objective: In the general population, girls have lower mortality risk compared to boys. However, few studies have focused on sex differences in survival and in access to kidney transplantation among children with end-stage renal disease (ESRD).

Study Design: Retrospective cohort study

Setting & Participants: Children aged 2 to 19 years registered in the United States Renal Data System (USRDS) who started renal replacement therapy (RRT) between 1995–2011.

Predictor of interest: Study participant sex

Outcome: Time to death, and time to kidney transplantation

Analytical Approach: We used adjusted Cox models to examine the association between sex and all-cause mortality. We used Fine-Gray models to examine the association between sex and kidney transplantation accounting for the competing risk of death.

Results: We included 14,024 children, of whom 1,880 died during 7.1 years of mean follow-up. In adjusted analyses, the hazard ratio for death was higher for girls (HR, 1.36; 95% CI, 1.25–1.50) than boys. When we further adjusted our survival models for transplantation as a time-dependent

Corresponding Author: Patrick Ahearn, MD, Address: 533 Parnassus Avenue, U404 Box 0532, San Francisco, CA 94143-0532, Fax: (415) 476-3381, patrick.ahearn@ucsf.edu.

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covariate, the hazard rate of death in girls was partially attenuated, but remained statistically significantly higher than that for boys (HR, 1.28; 95% CI, 1.17–1.41). Girls were also less likely to receive a kidney transplant than boys (adjusted sub-distribution HR, 0.91; 95% CI, 0.88–0.95) in analyses treating death as a competing risk.

Limitations: Lack of data on disease course prior to onset of RRT and observational study data.

Conclusions: The rate of mortality was substantially higher for girls than for boys treated with RRT. Access to transplantation was lower for girls than boys, but differences in transplantation access only accounted for a small proportion of the survival differences by sex.

Keywords

pediatric nephrology; sex disparity; mortality; kidney transplant; renal replacement therapy (RRT); end-stage renal disease (ESRD); girl; boy; children; mortality risk; incident ESRD; transplantation access; RRT modality

Introduction

Among adults in the United States, survival is better for women than men across all age groups.[1] However, the survival advantage of women compared to men in the general population has not been observed in the end-stage renal disease (ESRD) population. In fact, adult women with ESRD have similar mortality risk compared to men regardless of whether their treatment modality is dialysis or transplantation.[2–4]

Similarly, girls in the general population have better survival than boys.[1] However, a study of two small pediatric ESRD cohorts found no significant differences in the survival of girls versus boys with ESRD in the Netherlands.[5] One potential explanation for loss of the survival advantage of girls with ESRD is differences in access to kidney transplantation by sex, as transplantation improves survival of children with ESRD.[6–8] In adults, women are less likely to receive living and deceased donor transplanted kidneys than men,[9–11] but whether girls with ESRD have lower access to transplantation compared to boys has not been extensively studied.

The objectives of this study were to determine whether there are disparities in mortality risk by sex in the pediatric ESRD population and whether access to transplantation differs by sex or contributes to any mortality differences that may be present. We hypothesized that girls who undergo renal replacement therapy (RRT) would have similar if not higher mortality risk compared to boys, that girls would have lower access to transplantation compared to boys, and that lower access to transplantation would at least partially explain differences in survival among girls versus boys.

Methods

Study population

We performed a retrospective cohort study of children between the ages of 2 and 19 years who were followed between January 1, 1995 and June 30, 2012 using data from the United States Renal Data System (USRDS), the national ESRD registry. We included children

whose initial onset of ESRD (defined as receipt of preemptive transplant or long-term dialysis) fell within our study period, as evidenced by the availability of a Centers for Medicare & Medicaid Services ESRD Medical Evidence Report (Form CMS-2728-U3) filed within six months of the first ESRD service date (N=14,024, Figure 1). Children under the age of two were excluded, as standards for body mass indices (BMI) are not available for this age group from the Centers for Disease Control and Prevention (CDC), and BMI was a covariate of interest because of its known association with the likelihood of transplantation and risk of mortality in children.[12,13] Multiple imputation was performed using age, sex, race, insurance type, calendar year, and death with 50 repetitions for missing median income (n=454) and BMI (n=511) data.

Predictor and covariates of interest

Sex was abstracted from the Patients file in the USRDS. Patient demographic characteristics (age at incident ESRD, race), cause of ESRD, insurance coverage (Medicaid, none, or other) as an indicator of income status, zip code, date of ESRD onset, and BMI at incident ESRD were abstracted from the CMS-2728 form (MEDEVID) and Patients files of the USRDS as previously described.[13,14] BMI values were age- and sex- standardized to z-scores using the 2000 Centers for Disease Control and Prevention (CDC) standards for US children.[15] We defined underweight as BMI <5th percentile for age (corresponding to z-score <−1.64) and obese as BMI ≥95th percentile for age (corresponding to z-score ≥1.64) according to CDC criteria because of a known U-shaped association between BMI and mortality from prior studies in children treated with RRT.[12,13,16,17] We used zip code to determine median household income of patients' neighborhoods using values from the American Community Survey between 2006–2010 as a continuous variable.[18] Initial ESRD treatment modality (transplantation versus dialysis) was determined at the first ESRD service date as listed in the MEDEVID file. Creatinine values were abstracted from the Patient's files and used to calculate eGFR via the modified Schwartz equation.[19] Differences in the characteristics of children were compared between girls and boys using t-test, Mann-Whitney test, and chi-square test as appropriate.

Outcome ascertainment

We abstracted death dates and primary causes of death (categorized as cardiovascular, infectious, malignancy-related, or other) from the USRDS Patients file.

We determined the date of transplant procedures using USRDS Patient and Transplant files, which contain data reported by transplant centers to the United Network for Organ Sharing. We determined transplant donor source (living versus deceased) for first transplant using USRDS Patient and Transplant files.

Statistical analyses

Association between sex and risk of death—We assessed the association between patient sex and the hazard rate of all-cause mortality using a Cox proportional hazards model adjusted for age (as a continuous variable), cause of ESRD, Medicaid status, median neighborhood income, calendar year of ESRD onset (to account for potential secular trends in survival), and BMI category. We did not censor patients at the time of transplantation in

our primary analysis because transplantation is expected to improve outcomes and is a very common occurrence in children. We evaluated the hazard rate of death in subgroup analyses among those who were treated with dialysis versus transplantation as the first modality of RRT using adjusted Cox models.

In exploratory analyses, we assessed the potential association (sub-distribution hazard ratio [SHR]) between sex and risk of death attributed to different causes (cardiovascular, infectious, and malignancy) in separate adjusted Fine-Gray competing risk models for each cause of death, treating deaths from other causes as competing risks.

Association between sex and mortality in subgroup analyses—To determine whether sex disparities in survival may be amplified within particular subgroups, we tested for interactions between sex and pre-specified factors of interest including age (categorized as 2-<5 years, 5-<13 years and ≥13 years),[13] cause of ESRD, race, and calendar period of follow-up (before or after 2006 to assess for the potential effect of Share 35 implementation in September 2005).[20] We also tested for interaction according to initial dialysis modality (hemodialysis versus peritoneal dialysis), OPTN region, and insurance status.

Association between sex and time to transplantation—We assessed the association between sex and time to kidney transplantation, treating death as a competing risk in Fine-Gray models adjusted for age, race, cause of ESRD, Medicaid status, median income, BMI, and calendar year. In order to capture preemptive transplants in our model, we set transplantation to occur at 0.5 days after ESRD if transplantation was the initial ESRD treatment modality without any preceding dialysis. We also examined the odds of receiving a preemptive transplant using a logistic regression model adjusted for the same covariates as described above in girls compared to boys. To further explore potential sex-based disparities in kidney transplantation by donor type, we used Fine-Gray models adjusted for the same covariates to assess the risk of living transplant, accounting for the competing risk of death. In sensitivity analyses, we also treated deceased donor transplantation as a competing risk for living donor transplantation in our multi-variable Fine-Gray model.

Association between sex and mortality risk accounting for transplantation—To examine whether the association between sex and mortality risk was potentially attenuated by transplantation, we used the same multi-variable Cox proportional hazards model and further adjusted for transplantation as a time-dependent covariate.

With the exception of conversion of BMI into standardized BMI z-scores, which was performed using a Statistical Analysis System tool provided by the CDC,[15] all data analyses were conducted using STATA 14. The University of California Institutional Review Board considered this study exempt human subjects research. Informed consent was waived given that the research was not considered human subject research.

Results

Study cohort

We identified 14,024 children between the ages of 2 and 19 years who were initiated on RRT between 1995–2011. As shown in Table 1, there were significant differences in the characteristics of boys and girls at the time of initial RRT. Glomerulonephritis was significantly more common as a cause of ESRD in girls, whereas congenital abnormalities of the kidney and urinary tract (CAKUT) were more prevalent in boys. Girls were more likely to be uninsured at the time of ESRD onset or to have Medicaid as their insurer than boys. At the time of dialysis onset, girls had a mean eGFR (8.9 ml/min/1.73m^2 ± 5.5) that was significantly higher than that of boys (8.3 ml/min/1.73m^2 ± 4.9) ($p<0.001$). Mean albumin was significantly lower among girls (3.1 ± 0.8 g/dL) than boys (3.3 ± 0.9 g/dL) ($p<0.001$).

Mortality risk by sex

A total of 1,880 people died during 106,267 person-years of follow-up (median follow-up duration of 7.1 [IQR, 3.5–11.2] years). A total of 41,756 person-years of follow-up were attributable to time on dialysis and 64,511 person-years to time with a functional kidney transplant (Table 2). The overall mortality rate was 2.14 per 100 person-years for girls and 1.48 per 100 person-years for boys. The death rate was higher for girls compared to boys during both time attributed to dialysis and to transplantation (Table 2). In multi-variable analysis, the overall mortality risk for girls was 36% higher than that of boys (95% confidence interval [CI], 1.25–1.50, Table 3).

Cause of death differed significantly between sexes. Out of 1,880 deaths, 516 (27%) were attributed to cardiovascular cause, 257 (14%) to infectious cause, 68 (4%) to malignancy. In competing risk analysis, girls (compared to boys) had 1.33 (95% CI, 1.10–1.59) times higher risk of death attributed to cardiovascular causes, 1.14 (95% CI, 0.89–1.48) times higher risk of death attributed to infectious causes, and 1.13 (95% CI, 0.68–1.88) times higher risk of death attributed to malignancy.

We tested for the presence of interaction to determine whether the association between sex and mortality varied according to covariates of interest. We found a statistically significant interaction between sex and initial RRT modality: mortality risk was higher for girls (compared to boys) receiving either dialysis (HR, 1.33; 95% CI, 1.21–1.46) or transplantation (HR, 1.62; 95% CI, 1.07–2.46) as the initial mode of RRT (Table 3a).

We also found statistically significant interactions between sex and age, race, and initial modality of dialysis, but not with other covariates such as OPTN region. Specifically, disparities in mortality were more marked among girls compared to boys who were older (aged ≥13 years), black, or started RRT with hemodialysis (Figure 2).

Transplantation access by sex

To examine whether access to transplantation might explain these disparities, we first examined the amount of time spent with a functioning transplant according to sex. Boys spent 63% of the follow-up period with a functional allograft compared to girls, who spent

only 58% of follow-up time with a functional allograft (Table 2). In multi-variable Fine-Gray models treating death as a competing risk for transplant, girls had a lower risk of receiving a kidney transplant at any time during the follow-up period (subdistribution HR, 0.91; 95% CI, 0.88–0.95). Similar findings were noted among those who initiated RRT on dialysis (subdistribution HR, 0.94; 95% CI, 0.90–0.98; Table 3). Girls had a 21% lower odds [95% CI, 0.71–0.88] of receiving preemptive transplantation (Table 3). The likelihood for girls to undergo a living donor transplantation was 0.88 [95% CI, 0.84–0.94] times that of boys in Fine-Gray models treating death as a competing risk.

In models treating deceased donor transplantation as a competing risk for living donor transplantation, the likelihood for living donor transplantation in girls was 0.91 [95% CI, 0.86–0.96] times that of boys.

Adjustment for transplantation as a time-dependent variable

Finally, when we tested for whether differences in mortality risk would be further attenuated after accounting for access to transplant, we found that the higher mortality risk in girls was only slightly weakened from, from a HR of 1.36 [95% CI, 1.25–1.50] to 1.28 [95% CI, 1.17–1.41] but remained statistically significant (Table 3a).

Discussion

Survival is similar among adult women and men treated with renal replacement therapy; the survival advantage seen among women in the general population appears to be absent in the ESRD population.[2–4] In this study, we examined whether there were disparities in risk of death or transplantation access by sex among a large pediatric cohort of ESRD patients in the United States. Our data suggest that girls treated with RRT were at higher risk for death than boys. These disparities were especially notable among girls who were older (≥13 years of age) or black, and among girls treated with hemodialysis as the first RRT modality. The mortality difference between girls and boys with ESRD persisted even after accounting for demographic characteristics, cause of ESRD, BMI, and markers of socioeconomic status. We also found that girls had lower access to kidney transplantation, and especially to preemptive transplantation. Lower access to transplantation, however, did not substantially account for the survival differences among girls versus boys with ESRD.

Many factors may contribute to the observation that girls have lower survival than boys, including differences in the cause of kidney disease by sex, duration of earlier stages of CKD before reaching ESRD, presence of continued disease activity (e.g. for those with lupus nephritis) during the ESRD phase of illness, and differences in adherence to therapy by sex.[1,6,21,22] We did find a higher risk of cardiovascular- (compared to infectious- versus malignancy-) related deaths among girls. We speculate that girls may be more likely to have causes of ESRD that are associated with greater degrees of inflammation (such as lupus nephritis) than boys, and exposure to long-term inflammation may be associated with greater long-term risk of cardiovascular disease and mortality.[23–26] A study performed by Adams and colleagues also previously demonstrated that women on dialysis, especially younger women between 18–34 years of age, were hospitalized more frequently than men.[27] In the Adams study, women with ESRD also had lower serum albumin levels than men, and prior

studies have shown that lower albumin is associated with higher mortality risk after dialysis initiation.[28] Our observation of statistically significantly lower albumin levels at time of ESRD onset in girls compared to boys is consistent with these findings in adults. We also found the sex-based disparities in mortality risk were especially notable among adolescent children treated with ESRD (compared to younger children). Given the greater likelihood of medication nonadherence during the teenage years and the potential for pregnancy, which may increase the risk of rejection, graft failure, and therefore death, these factors may have contributed to the disparities in survival that we observed in our study.[22,29,30]

A number of factors may contribute to the observation of lower transplantation access in girls compared to boys. Given the differences in cause of ESRD between boys and girls, with boys being more likely to have congenital anomalies, it is likely that boys were diagnosed with kidney disease at an earlier age (and even *in utero* during prenatal ultrasound screening).[31,32] With earlier diagnosis, boys may obtain routine nephrology care at an earlier time point in their disease and may therefore have better access to kidney transplantation, and especially preemptive transplantation, than girls. A study of timing of ESRD therapy by Hogan et al. in a European cohort also found that girls had less nephrology care prior to the initiation of RRT and lower access to preemptive transplantatoin.[6] The lower albumin levels at the time of ESRD onset that we observed among girls may reflect greater levels of proteinuria and faster rates of CKD progression, which may have led to less time for potential workup of donors for preemptive or living donor transplantation.[33,34] The exact reasons for the observed tendency toward lower access to living donor transplantation among girls compared to boys remain unclear but deserve further study.

Despite the disparity in transplantation access by sex, we found that access to transplantation was a small contributor to the survival differences between girls versus boys treated with ESRD. These findings differ from the racial disparities in survival among children with ESRD that we noted in a prior study, where lower access to transplantation among black (versus white) children appeared to explain the worse survival among black children treated with RRT.[14]

The strengths of our study include the use of a large nationally representative cohort of children with ESRD with a large number of clinical outcomes during almost two decades of follow-up. Limitations include the observational nature of our data, missing covariates and causes of death, potential limitations in the validity of reported causes of death, and lack of more granular data on barriers to preemptive transplantation and living donation among girls. We do not have trajectories of kidney disease progression prior to onset of ESRD or level of adherence to therapy, which may have contributed to the observed sex disparities in outcomes. Finally, we cannot exclude the possibility of residual confounding.

In conclusion, we found that girls treated with RRT had a significantly higher risk of death than boys, especially from cardiovascular causes of death. Of concern, girls were also less likely to receive kidney transplantation (both from living and deceased donors) compared to boys. However, the disparity in mortality risk was only partially attenuated when accounting for sex disparities in access to transplantation. Understanding why sex disparities in survival and access to transplantation are present in children is important, given that children should

have better access to health care and higher priority on the kidney transplant waitlist than adults. Further studies are needed to address differences in mortality risk by sex and to ensure equity of access to kidney transplantation in order to improve outcomes in all children with ESRD.

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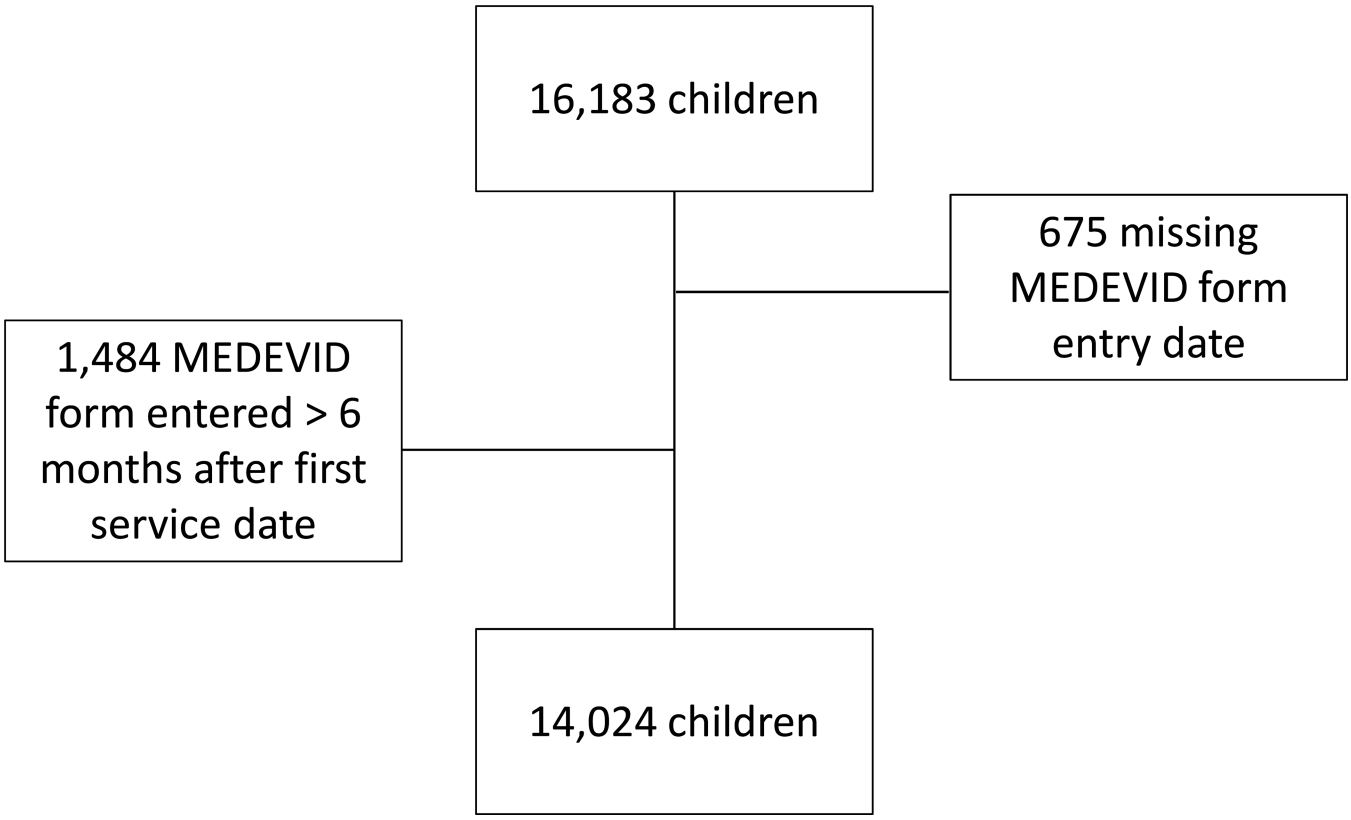

Figure 1.
Derivation of cohort included for analysis.

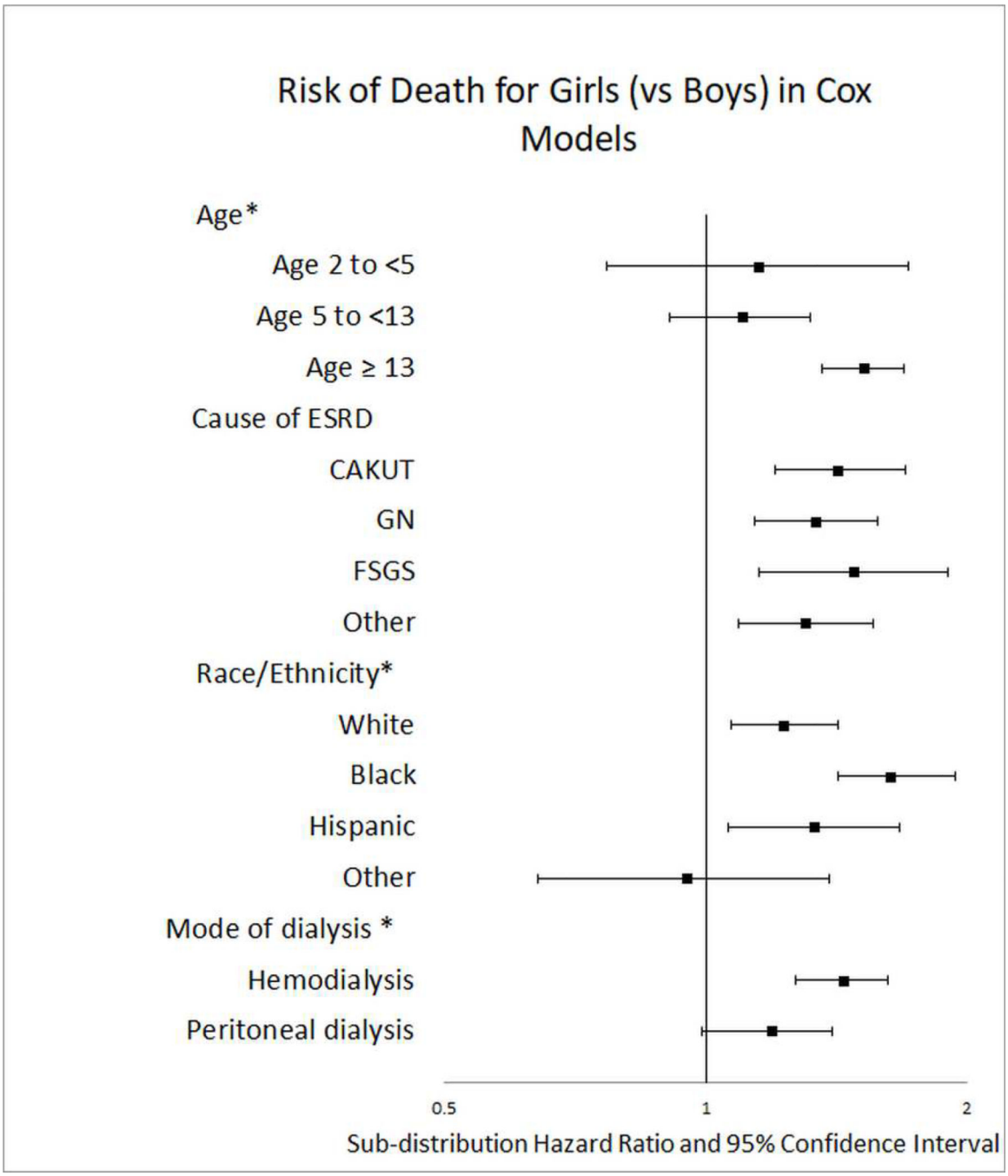

Figure 2.

Risk of death for girls (versus boys) in cox models, by covariates of interest. CAKUT, congenital anomalies of the kidney and urologic tract; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HD, Hemodialysis; PD Peritoneal dialysis

[1] All models adjusted for age, race, cause of ESRD, calendar year, insurance type, median neighborhood income, and BMI z-score category unless otherwise specified.

* test for interaction with $p<0.05$

Table 1:

Characteristics of boys and girls with ESRD.

Characteristic	Boys (n=7,689)	Girls (n=6,335)	p-value
age in years	14.5 [10.5–17.5]	14.5 [11.5–17.5]	0.5
Race[1] % (N)			0.4
White	45.7 (3,517)	44.6 (2,824)	
Black	23.0 (1,771)	23.0 (1,459)	
Hispanic	23.9 (1,834)	24.8 (1,572)	
Other	7.4 (567)	7.5 (478)	
Cause of ESRD[2] % (N)			<0.001
CAKUT	44.5 (3,420)	31.9 (2,019)	
Glomerulonephritis	19.5 (1,500)	32.0 (2,028)	
FSGS	15.0 (1,154)	14.4 (915)	
Other	20.8 (1,597)	21.5 (1,361)	
Insurance % (N)			0.002
None	7.3 (563)	7.5 (474)	
Medicaid	44.3 (3,408)	47.1 (2,986)	
Other	48.4 (3,718)	45.4 (2,875)	
income[3] $	48,272 [38,097–62,909]	47,379 [37,410–62,106]	0.008
Mode of RRT[4] % (N)			<0.001
Hemodialysis	50.7 (3,897)	52.9 (3,349)	
Peritoneal dialysis	30.6 (2,356)	33.6 (2,131)	
Preemptive transplantation	17.6 (1,353)	12.3 (777)	
BMI category[5] % (N)			0.7
Underweight	10.2 (788)	9.9 (628)	
Normal weight	68.6 (5,274)	69.4 (4,396)	
Obese	17.3 (1,328)	17.3 (1,099)	

N=14,024. Values shown for continous variables are given as median [interquartile range]; for categorical variables, as count (percentage).

ESRD, end-stage renal disease; CAKUT, congenital anomalies of the kidney and urologic tract; RRT, renal replacement therapy; eGFR, estimated glomerular filtration rate; BMI, body mass index

[1]Missing in N=2 (0 boys, 2 girls)

[2]Missing in N=30 (18 boys, 12 girls)

[3]Missing in N=454 (268 boys, 186 girls)

[4]Missing in N=161 (83 boys, 78 girls)

[5]Missing in N=511 (299 boys, 212 girls)

Table 2.

Follow-up and outcomes partitioned between dialysis and transplant follow-up time according to sex.

	Dialysis (41,756 person-years)	Transplant (64,511 person-years)
Boys		
Follow-up time, person-years (% of total)	22,142 (37)	37,027 (63)
Deaths	692	183
Death rate (per 100 person- years)	3.13	0.49
Girls		
Follow-up time, person-years (% total time)	19,614 (42)	27,304 (58)
Deaths (N)	834	171
Death rate (per 100 person- years)	4.25	0.63
Adjusted HR (95% CI) of all-cause mortality (girls vs. boys)*	1.29 (1.16–1.43)	1.25 (1.01–1.55)

*Adjusted for age, race, cause of ESRD, calendar year, insurance type, median neighborhood income, and BMI zscore category unless otherwise specified.

Table 3:

Hazard ratio for death and transplantation after RRT onset by sex.

	HR or OR for Girls (vs Boys)
Death after RRT onset, by sex	
Cox proportional hazards models[1]	
Unadjusted model (n=14,024)	1.45 (1.32–1.58)
Adjusted model (n=14,024)	1.36 (1.25–1.50)
Dialysis as first RRT (n=11,894)	1.33 (1.21–1.46)
Preemptive transplantation (n=2,130)	1.62 (1.07–2.46)
Adjusted model with transplantation as time-dependent covariate (n=14,024)	1.28 (1.17–1.41)
Transplantation after RRT onset, by sex	
Fine-Gray competing risk models[2]	
Unadjusted model (n=14,024)	0.86 (0.83–0.89)
Adjusted model (n=14,024)	0.91 (0.88–0.95)
Dialysis as first RRT (n=11,894)	0.94 (0.90–0.98)
Living donor transplantation (n=14,024)	0.88 (0.84–0.94)
Logistic regression models	
Preemptive transplanation[3] (n=14,024)	0.79 (0.71–0.88)

RRT, renal replacement therapy; HR, hazard ratio; OR, odds ratio

[1]Values shown are hazard ratio (95% confidence interval). All models adjusted for age, race, cause of ESRD, calendar year, insurance type, median neighborhood income, and BMI z-score category unless otherwise specified.

[2]Values shown are subdistribution hazard ratio (95% confidence interval). Models adjusted for age, race, cause of ESRD, calendar year, insurance type, median neighborhood income, and BMI z-score category with death treated as a competing risk for transplant.

[3]Values shown are odds ratio (95% confidence interval). Preemptive transplantation defined as first transplantation date equal to first ESRD service date. Model adjusted for age, race, cause of ESRD, calendar year, insurance type, median neighborhood income, and BMI z-score category.