Title

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Journal

American journal of kidney diseases : the official journal of the National Kidney Foundation, 73(6)

ISSN

0272-6386

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Publication Date

2019-06-01

DOI

10.1053/j.ajkd.2018.12.038

Estimated GFR at Dialysis Initiation and Mortality in Children and Adolescents

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Rationale & Objective: The association of estimated glomerular filtration rate (eGFR) at dialysis therapy initiation with mortality among adult dialysis patients has been greatly debated, with some studies showing no benefit from early dialysis therapy initiation. However, this association has not been well investigated in pediatric dialysis patients. The objective of this study was to evaluate the mortality risk associated with eGFR at dialysis therapy initiation in children and adolescents with kidney failure.

Study Design: Retrospective cohort study.

Setting & Participants: 9,963 incident dialysis patients aged 1 to 17 years in the US Renal Data System registry (1995-2016).

Predictor: eGFRs at dialysis therapy initiation calculated using the pediatric-specific bedside Schwartz equation (<5, 5-<7, 7-<9, 9-<12, and ≥12 mL/min/1.73 m^2).

Outcome: Time to all-cause death.

Analytical Approach: Cox proportional hazards regression adjusted for case-mix variables, height, body mass index, hemoglobin level, and serum albumin level.

Results: Median eGFR was 7.8 (IQR, 5.6-10.5) mL/min/1.73 m^2 and median age was 13 (IQR, 9-16) years. 696 deaths were observed during the median follow-up of 1.4 (IQR, 0.7-2.7) years, and overall crude mortality rate was 31 per 1,000 patient-years. There appeared to be a trend toward higher mortality risk across higher eGFRs at dialysis therapy initiation. Compared with eGFRs of 7 to <9 mL/min/1.73 m^2, eGFRs <5 and ≥12 mL/min/1.73 m^2 were associated with lower and higher mortality, with adjusted HRs of 0.57 (95% CI, 0.43-0.74) and 1.31 (95% CI, 1.05-1.65), respectively. In age-stratified analysis, there were consistent relationships among patients 6 years and older while the eGFR-mortality association was attenuated among patients younger than 6 years ($P_{interaction}$ = 0.002).

Limitations: Possible errors in eGFRs due to methods for serum creatinine measurement. Unmeasured confounders related to eGFR at dialysis therapy initiation.

Conclusions: Higher eGFR at dialysis therapy initiation was associated with higher mortality risk. Further studies of eGFR at initiation are needed in pediatric dialysis patients, especially among those younger than 6 years.

Complete author and article information provided before references.

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Am J Kidney Dis. 73(6): 797-805. Published online March 2, 2019.

doi: 10.1053/j.ajkd.2018.12.038

In both children and adults with chronic kidney disease (CKD), estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2 typically calls for renal replacement therapy.[1-3] Despite being a standard parameter in the consideration of dialysis therapy initiation, eGFR is not an independent determinant for the timing of dialysis therapy initiation.[4] In both children and adult patients with CKD, other indications for dialysis therapy initiation consist of clinical and biochemical characteristics, including fluid, nutritional, and uremic status, in addition to eGFR.[5] Nevertheless, eGFR is still a useful and important parameter in combination with those other factors in determining the timing of dialysis therapy[6] and is often the center of focus in clinical practice.[7]

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A number of observational studies have shown an association between higher eGFR at dialysis therapy initiation and higher mortality in adult patients with end-stage renal disease (ESRD).[8-13] Moreover, some of these studies have also suggested an association between lower eGFRs and lower mortality risk.[8-11] A randomized controlled trial suggested that early dialysis therapy initiation may not be associated with improvement of survival in adults.[14] Accordingly, there seems to be no independent benefit of dialysis therapy initiation at higher eGFRs. Additionally, these studies raise the question of whether dialysis therapy initiation at even lower eGFRs may be safe, if not beneficial, to adult patients.[6]

Contrary to the growing body of research in adult dialysis patients, there is little research investigating eGFRs and dialysis therapy timing in children receiving dialysis. In the 2000s, median eGFRs at the start of renal replacement therapy were 10.4 and 8.5 mL/min/1.73 m^2 among pediatric patients in Europe[15] and the United States,[16] respectively. Younger age, female sex, and black race were predictors for dialysis therapy initiation at lower eGFRs in children.[15,17] A cohort study using data from the US Renal Data System (USRDS) showed that eGFRs > 15 mL/min/1.73 m^2 had lower risk for hospitalization for hypertension or pulmonary edema compared to ≤15 mL/min/1.73 m^2 in 4,772 children on dialysis therapy.[18]

However, the association between eGFR at dialysis therapy initiation and mortality in children dialysis patients remains unknown.

Therefore, we conducted a retrospective cohort study using data from the USRDS to investigate the relationship of eGFR at dialysis therapy initiation and risk for mortality in children receiving dialysis. We also examined which patients' characteristics are predictors of high (≥12 mL/min/1.73 m^2) and low (<5 mL/min/1.73 m^2) eGFRs at dialysis therapy initiation.

Methods

Study Approval

This study was approved by the Institutional Review Board of University of California Irvine with a waiver of informed consent because the USRDS contains only deidentified information.

Calculation of eGFR at Dialysis Initiation and Study Population

We calculated eGFRs at dialysis therapy initiation using the pediatric-specific Schwartz formula.[19] Height was obtained from the Centers for Medicare & Medicaid Services (CMS) Medical Evidence form (CMS2728) completed within ±6 months of the first dialysis date. Furthermore, data for serum creatinine (Scr) level were restricted to those obtained within 3 months before the first dialysis date. The median lag time between the first dialysis date and date of Scr obtained was −3 (interquartile range [IQR], −9 to 0) days. We excluded patients with height *z* scores of −5 or less or >5 and eGFRs ≥ 30 mL/min/1.73 m^2 from analyses because those values are likely erroneous given the patient population. We categorized eGFRs into 5 groups: <5, 5 to <7, 7 to <9, 9 to <12, and ≥12 mL/min/1.73 m^2 for analyses.

A total of 13,172 patients who were 1 to 17 years old and initiated dialysis therapy between April 1, 1995, and April 30, 2016, were identified from the USRDS. Among these eligible patients, we excluded 240 patients who received dialysis for less than 60 days, 678 patients whose CMS2728 was not completed by the physician within ±6 months of dialysis therapy initiation, 1,626 patients who had missing Scr values within 3 months before dialysis therapy initiation, 539 patients who had missing height or height *z* scores of −5 or less or >5, and 126 patients who had eGFRs ≥ 30 mL/min/1.73 m^2 (Fig 1).

Patients were followed up from dialysis therapy initiation and censored for transplantation, loss to follow-up, discontinuing dialysis therapy, or the end of follow-up (10 years after dialysis therapy initiation or June 30, 2016), whichever occurred first.

Data Source

Information for Scr level, height, death, transplantation, age at initiation of dialysis therapy, sex, race, ethnicity, Medicaid use, initial dialysis modality, primary cause of ESRD, year of dialysis therapy initiation, comorbid conditions, body mass index (BMI), hemoglobin level, and serum albumin level was obtained from the Patients file (PATIENTS); the Treatment History file (RXHIST); the Medical Evidence file (MEDEVID), which contains data from the CMS2728; and the Transplant file (TX) in the USRDS.

Height and BMI values were age- and sex-standardized to *z* scores using the 2000 Centers for Disease Control and Prevention Growth Chart.

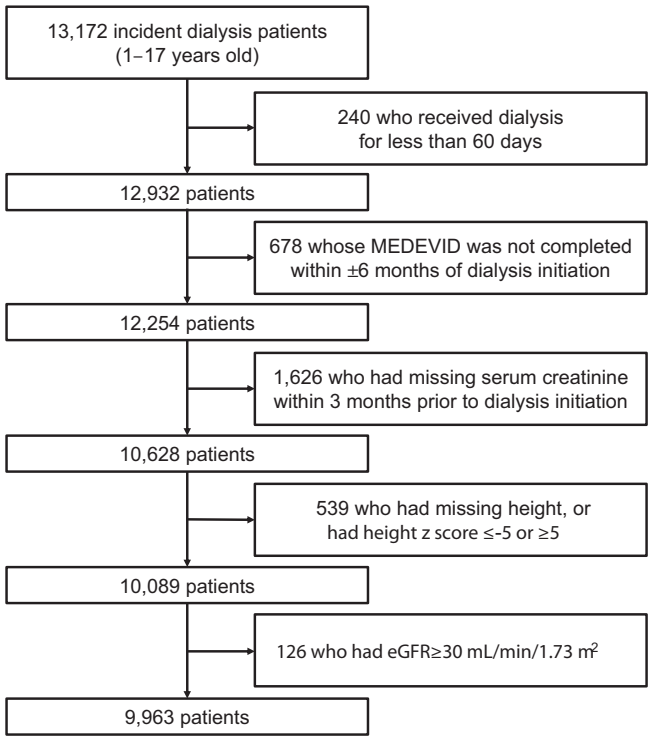

Figure 1. Cohort construction. Abbreviation: eGFR, estimated glomerular filtration rate.

Statistical Analysis

Characteristics at the time of dialysis therapy initiation are summarized across eGFR categories and expressed as frequency (proportions), mean ± standard deviation, or median and IQR, as appropriate. Trends across eGFR categories were evaluated using nonparametric trend tests or linear regressions. Differences between included and excluded patients were compared using standardized differences due to the large sample size of this study. We examined independent associations of all variables with the highest (≥12 mL/min/1.73 m^2) and lowest (<5 mL/min/1.73 m^2) eGFRs at dialysis therapy initiation using adjusted multinomial logistic regression.

The primary outcome was all-cause mortality. We used Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality risk associated with eGFR at dialysis therapy initiation. We examined risk for mortality in unadjusted, case-mix–adjusted, and fully adjusted models. The unadjusted model consisted of eGFR categories at dialysis therapy initiation. The

case-mix–adjusted model included categorized eGFR plus age at dialysis therapy initiation, sex, race (white, black, and other races), ethnicity (Hispanic or non-Hispanic), Medicaid coverage as an indicator of lower income status, initial dialysis modality (hemodialysis, peritoneal dialysis, and unknown), primary cause of ESRD (congenital anomalies of the kidney and urinary tract [CAKUT] or non-CAKUT), the year in which dialysis therapy was started, and comorbid conditions (hypertension, heart disease, nonrenal anomaly, malignancy, and diabetes). The fully adjusted model included height z score, BMI z score, hemoglobin level, and serum albumin level in addition to all covariates in the case-mix model. eGFR was further modeled as a continuous variable, and its association with mortality was estimated using restricted cubic spline function with 4 knots placed at the 5th, 35th, 65th, and 95th percentile of eGFR. As sensitivity analyses, we calculated eGFR using the original Schwartz formula[20] and performed the same analyses in 4,764 patients who started dialysis therapy between 1995 and 2004 because Scr was mainly measured using the Jaffé method[21] and eGFR was calculated using the original Schwartz formula during this period.

We examined potential effect modification of the association between eGFR and mortality by all case-mix variables by including interaction terms in Cox regression models, and $P_{interaction} < 0.05$ was considered to indicate an effect modification. Then we performed subgroup analysis according to those case-mix variables. In subgroup analysis, we categorized age and incident year into younger than 6 and 6 years or older and incident years 1995 to 1999, 2000 to 2004, 2005 to 2009, and 2010 to 2016, respectively. The frequency of missing data was 5%,

Table 1. Characteristics at Dialysis Initiation

		eGFR, mL/min/1.73 m²					
	All	<5	5-<7	7-<9	9-<12	≥12	*P*
No. of patients	9,963	1,871 (19%)	2,152 (22%)	2,242 (23%)	2,011 (20%)	1,687 (17%)	
Age, y	13 [9-16]	14 [11-16]	13 [9-16]	14 [9-16]	13 [10-16]	13 [8-15]	<0.001
Age category							
<6 y	1,263 (13%)	167 (9%)	265 (12%)	285 (13%)	260 (13%)	286 (17%)	<0.001
6-<13 y	2,907 (29%)	489 (26%)	685 (32%)	640 (29%)	594 (30%)	499 (30%)	0.06
≥13 y	5,793 (58%)	1,215 (65%)	1,202 (56%)	1,317 (59%)	1,157 (58%)	902 (53%)	<0.001
Male sex	5,266 (53%)	1,030 (55%)	1,091 (51%)	1,233 (55%)	1,099 (55%)	813 (48%)	0.007
Race							
White	6,471 (65%)	1,124 (60%)	1,399 (65%)	1,425 (64%)	1,352 (67%)	1,171 (69%)	<0.001
Black	2,812 (28%)	607 (32%)	590 (27%)	674 (30%)	544 (27%)	397 (24%)	<0.001
Other	680 (7%)	140 (7%)	163 (8%)	143 (6%)	115 (6%)	119 (7%)	0.1
Hispanic	2,828 (28%)	585 (31%)	621 (29%)	627 (28%)	553 (27%)	442 (26%)	<0.001
Medicaid use	5,237 (53%)	792 (42%)	1,101 (51%)	1,249 (56%)	1,119 (56%)	976 (58%)	<0.001
Dialysis type							
HD	5,313 (53%)	1,057 (56%)	1,119 (52%)	1,216 (54%)	1,014 (50%)	907 (54%)	0.02
PD	4,581 (46%)	802 (43%)	1,014 (47%)	1,012 (45%)	980 (49%)	773 (46%)	0.02
Uncertain	69 (1%)	12 (1%)	19 (1%)	14 (1%)	17 (1%)	7 (0%)	0.6
CAKUT	2,394 (24%)	424 (23%)	506 (24%)	595 (27%)	520 (26%)	349 (21%)	0.9
Incidence year							
1995-1999	2,027 (20%)	550 (29%)	585 (27%)	482 (21%)	261 (13%)	149 (9%)	<0.001
2000-2004	2,597 (26%)	522 (28%)	631 (29%)	620 (28%)	502 (25%)	322 (19%)	<0.001
2005-2009	2,442 (25%)	437 (23%)	473 (22%)	567 (25%)	543 (27%)	422 (25%)	0.02
2010-2016	2,897 (29%)	362 (19%)	463 (22%)	573 (26%)	705 (35%)	794 (47%)	<0.001
Comorbid conditions							
Hypertension	4,267 (43%)	736 (39%)	882 (41%)	965 (43%)	914 (45%)	770 (46%)	<0.001
Heart disease	402 (4%)	79 (4%)	66 (3%)	98 (4%)	64 (3%)	95 (6%)	0.1
Nonrenal anomaly	306 (3%)	29 (2%)	59 (3%)	55 (2%)	75 (4%)	88 (5%)	<0.001
Malignancy	148 (1%)	8 (0%)	24 (1%)	36 (2%)	30 (1%)	50 (3%)	<0.001
Diabetes	150 (2%)	16 (1%)	25 (1%)	42 (2%)	34 (2%)	33 (2%)	0.002
Height *z* score	−1.0 ± 1.5	−0.9 ± 1.5	−1.1 ± 1.6	−1.1 ± 1.5	−1.0 ± 1.5	−1.0 ± 1.6	0.5
BMI *z* score	0.2 ± 1.5	0.2 ± 1.4	0.2 ± 1.5	0.2 ± 1.4	0.2 ± 1.5	0.2 ± 1.5	0.7
Hemoglobin, g/dL	9.4 ± 2.4	7.9 ± 2.3	9.3 ± 2.6	9.8 ± 2.2	10.0 ± 2.0	10.0 ± 2.3	<0.001
Albumin, g/dL	3.2 ± 0.9	3.2 ± 0.7	3.3 ± 0.9	3.3 ± 0.9	3.3 ± 0.9	3.1 ± 1.0	0.001

Note: Values for categorical variables are given as frequency (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range]. Trends across eGFR categories were evaluated by nonparametric trend tests or linear regressions.

Abbreviations: BMI, body mass index; CAKUT, congenital anomaly of the kidney and urinary tract; eGFR, estimated glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis.

8%, and 16% for BMI, hemoglobin level, and serum albumin level, respectively. We performed multiple imputation using multivariate normal regression. We included case-mix variables in the imputation model using 15 imputed data sets.[22] The estimates were combined using Rubin's rules.[23,24] Analyses were performed using STATA MP, version 13.1 (Stata Corp).

Results

Patient Characteristics

A total of 9,963 incident pediatric dialysis patients were included for analysis. In the final cohort, median eGFR was 7.8 (range, 1.4-29.9) mL/min/1.73 m^2 and median age was 13 (IQR, 9-16) years. Children initiating therapy with a higher eGFR were more likely to be white, use Medicaid, and have hypertension, nonrenal anomaly, malignancy, and greater hemoglobin levels. They were also less likely to be black race and of Hispanic ethnicity (Table 1). Across calendar years 1995 to 2016, there was a secular increase and decrease was observed in eGFR and Scr levels at dialysis therapy initiation, respectively (Fig 2; Table S1). Height, which was used to calculate eGFR, and Scr levels showed no particular trend across years.

Likelihood of eGFR < 5 and ≥12 mL/min/1.73 m^2 at Dialysis Initiation

After full adjustment, age 13 years or older (vs <6 years), male sex, black race (vs white), Hispanic ethnicity, non-Medicaid coverage, incidence year between 1995 and 1999 (vs other years), absence of malignancy and diabetes as comorbid conditions, and lower hemoglobin level were all associated with eGFR < 5 (reference, 5 to <12) mL/min/1.73 m^2 (Table 2). In addition, age younger than 6 years (vs ≥13 years), female sex, white race (vs black), non-Hispanic ethnicity, incidence year between 2000 and 2016 (vs 1995-1999), presence of heart disease and malignancy as comorbid conditions, higher height stature, higher hemoglobin level, and lower serum albumin level were associated with eGFR ≥ 12 (reference, 5 to <12) mL/min/1.73 m^2.

In sensitivity analysis examining a subgroup of 4,764 patients who were incident between 1995 and 2004 using the original Schwartz equation, this positive association across eGFR strata was consistent in white race, non-Hispanic ethnicity, malignancy, and hemoglobin level (Table S2). However, patients younger than 6 years were less likely to start dialysis therapy at either eGFRs < 5 or ≥12 mL/min/1.73 m^2, and male patients were more likely to start dialysis therapy at eGFRs ≥ 12 mL/min/1.73 m^2 and less likely to start at <5 mL/min/1.73 m^2. When we calculated eGFR using the 2009 Schwartz formula in this subcohort of 4,764 patients incident from 1995 to 2004, the association observed in patients younger than 6 years and males was consistent with our overall analysis. The fully adjusted odds ratios for eGFR < 5 and ≥12 mL/min/1.73 m^2 were 0.76 (95% CI, 0.59-0.99) and 1.40 (95% CI, 1.03-1.89) in patients younger than 6 years and 1.24 (95% CI, 1.07-1.44) and 0.81 (95% CI, 0.67-0.99) in male patients, respectively.

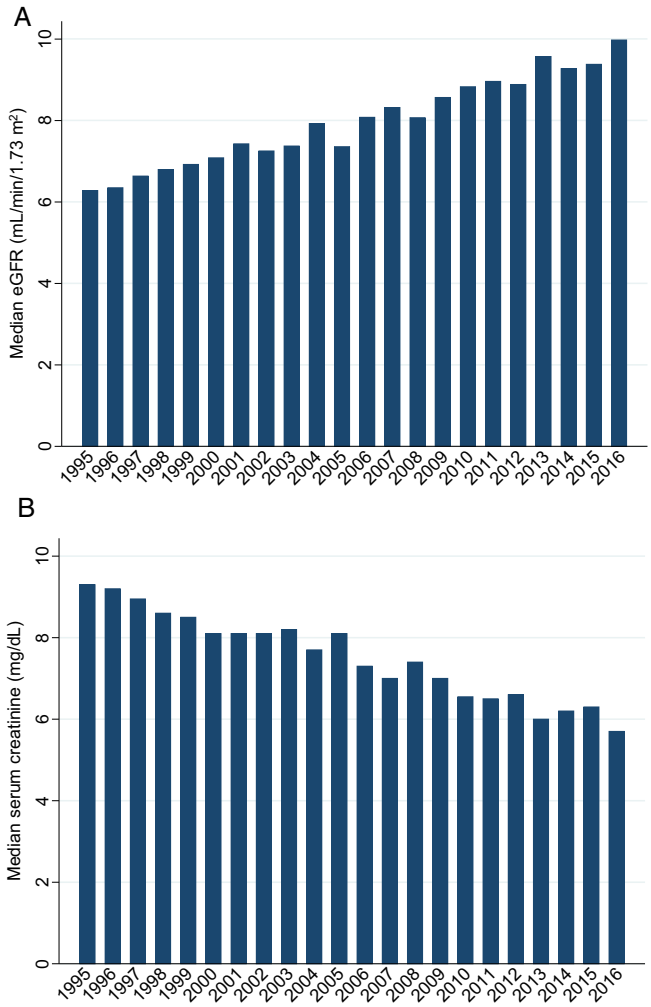

Figure 2. Secular trends in (A) estimated glomerular filtration rate (eGFR) and (B) serum creatinine level.

Mortality Across eGFRs at Dialysis Initiation

A total of 696 deaths were observed during a total follow-up of 22,611 patient-years. The overall crude mortality rate was 31 per 1,000 patient-years. Mortality rates were 19, 31, 32, 32, and 43 per 1,000 patient-years for eGFRs <5, 5 to <7, 7 to <9, 9 to <12, and ≥12 mL/min/1.73 m^2, respectively. Information for cause of death was available for 636 (91%) patients, and cardiovascular disease (34%), infection (17%), and malignancy (4%) were the leading causes (Table S3). The proportion of cardiovascular-related deaths increased with advancing age, while that of malignancy was high at a younger age. Although there were no remarkable trends across eGFRs, the proportion of cardiovascular-related deaths was slightly higher for eGFRs < 5 mL/min/1.73 m^2.

Table 2. Likelihood of eGFR < 5 and ≥12 mL/min/1.73 m^2 at Dialysis Initiation in the Fully Adjusted Model

	OR (95% CI)	
	eGFR < 5 mL/min/1.73 m^2	eGFR ≥ 12 mL/min/1.73 m^2
Age		
<6 y	0.69 (0.57-0.84)	1.40 (1.18-1.66)
6-<13 y	0.78 (0.69-0.89)	1.05 (0.93-1.20)
≥13 y	1.00 (reference)	1.00 (reference)
Male sex (vs female)	1.27 (1.13-1.42)	0.81 (0.73-0.91)
Race		
White	1.00 (reference)	1.00 (reference)
Black	1.45 (1.26-1.66)	0.70 (0.61-0.81)
Other	1.20 (0.97-1.50)	0.96 (0.77-1.20)
Hispanic (vs non-Hispanic)	1.39 (1.21-1.59)	0.80 (0.70-0.91)
Medicaid use (vs non-Medicaid use)	0.64 (0.57-0.72)	1.10 (0.98-1.23)
Dialysis type		
HD	1.00 (reference)	1.00 (reference)
PD	0.96 (0.86-1.08)	0.92 (0.82-1.04)
Uncertain	0.92 (0.46-1.83)	0.53 (0.24-1.21)
CAKUT (vs non-CAKUT)	1.07 (0.93-1.24)	0.89 (0.76-1.03)
Incidence year		
1995-1999	1.00 (reference)	1.00 (reference)
2000-2004	0.80 (0.69-0.93)	1.62 (1.31-2.00)
2005-2009	0.78 (0.66-0.91)	2.34 (1.90-2.87)
2010-2016	0.60 (0.51-0.70)	4.11 (3.38-5.00)
Comorbid conditions		
Hypertension	0.92 (0.82-1.03)	0.93 (0.83-1.04)
Heart disease	1.13 (0.85-1.51)	1.42 (1.10-1.84)
Nonrenal anomaly	0.77 (0.51-1.18)	1.23 (0.94-1.62)
Malignancy	0.37 (0.18-0.79)	1.66 (1.15-2.40)
Diabetes	0.55 (0.31-0.95)	1.10 (0.73-1.67)
Height *z* score, per 1 point greater	1.01 (0.98-1.05)	1.06 (1.02-1.10)
BMI *z* score, per 1 point greater	1.04 (1.00-1.08)	0.97 (0.93-1.01)
Hemoglobin, per 1 g/dL greater	0.69 (0.67-0.71)	1.09 (1.06-1.11)
Albumin, per 0.5 g/dL greater	1.02 (0.98-1.06)	0.88 (0.85-0.91)

Note: Reference: eGFR 5 to <12 mL/min/1.73 m^2.
Abbreviations: BMI, body mass index; CAKUT, congenital anomaly of the kidney and urinary tract; CI, confidence interval; eGFR, estimated glomerular filtration rate; HD, hemodialysis; OR, odds ratio; PD, peritoneal dialysis.

There was an incrementally higher mortality risk across higher eGFRs (P_{trend} < 0.001 for all adjustments), for which fully adjusted HRs were 0.57 (95% CI, 0.43-0.74) and 1.31 (95% CI, 1.05-1.65) for eGFRs < 5 and ≥12 mL/min/1.73 m^2, respectively (reference: eGFR 7 to <9 mL/min/1.73 m^2; Fig 3). This association was robust in restricted cubic spline models across all levels of adjustment (Fig S1). Age was a potential effect modifier in the association between eGFR and mortality ($P_{interaction}$ = 0.002). Although the association between eGFR and mortality was consistent with the overall analysis in patients 6 years and older, there appeared to be no difference in mortality risk across eGFRs in those younger than 6 years, though this group comprised only 1,263 patients (Fig 4). In subgroup analysis, lower mortality for eGFRs < 5 mL/min/1.73 m^2 and higher mortality for eGFRs ≥ 12 mL/min/1.73 m^2 compared with eGFRs of 5 to <12 mL/min/1.73 m^2 were observed in most subgroups ($P_{interaction}$ > 0.05 for all; Fig 5). Although mortality for eGFRs < 5 mL/min/1.73 m^2 was comparable to that of eGFRs of 5 to <12 mL/min/1.73 m^2 in patients with CAKUT (n = 2,394), the test for interaction did not show effect modification ($P_{interaction}$ = 0.2).

Moreover, a similar linear association between eGFR and mortality risk was observed among patients who started dialysis therapy between 1995 and 2004 with eGFRs calculated using the original Schwartz formula (Fig S2).

Discussion

In a cohort of 9,963 children with kidney failure, there was a secular increase in eGFRs at dialysis therapy initiation from 1995 to 2016. We observed a linear association between eGFR at dialysis therapy initiation and mortality, which was robust across all adjustment models. In particular, eGFRs < 5 and ≥12 mL/min/1.73 m^2 were associated with lower and higher mortality risks, respectively. This association was consistent in subgroup analyses by sex, race, ethnicity, use of Medicaid, initial dialysis modality, and the year in which dialysis therapy was started. The association between eGFR and mortality was modified by age, for which the lower and higher mortality risk associated with eGFRs < 5 and ≥12 mL/min/1.73 m^2 was attenuated in patients younger than 6 years.

Our observation of higher eGFR associated with higher mortality risk was consistent with many previous studies investigating adult patients with kidney failure.[25] Potential mechanisms of harm from dialysis therapy initiation at higher eGFRs may be explained by hemodynamic fluctuations, exposure to high glucose concentrations, removal of vitamins and minerals, and rapid loss of residual kidney function,[26] which are also applicable and observed in both children and adult dialysis patients.[27] More importantly, there is difficulty in the estimation of dry weight in children, which may further promote the harmful aspects of dialysis.[28]

The lower mortality risk observed for eGFRs < 5 mL/min/1.73 m^2 in our cohort should be highlighted as well. Dialysis therapy initiation at lower eGFRs has some benefits, including cost savings and quality-of-life considerations.[29-31] Despite the secular trend of increasing eGFRs at dialysis therapy initiation,[6,32] studies (including the present study) show favorable outcomes with dialysis therapy initiation at lower eGFRs. However, it should be noted that a lower eGFR at dialysis therapy initiation may also reflect favorable general conditions that allow deferring the timing of dialysis therapy initiation.[8,9] Due to the availability of data in the USRDS database, we could only incorporate certain variables regarding general conditions in our analyses, such as height, BMI, and serum albumin

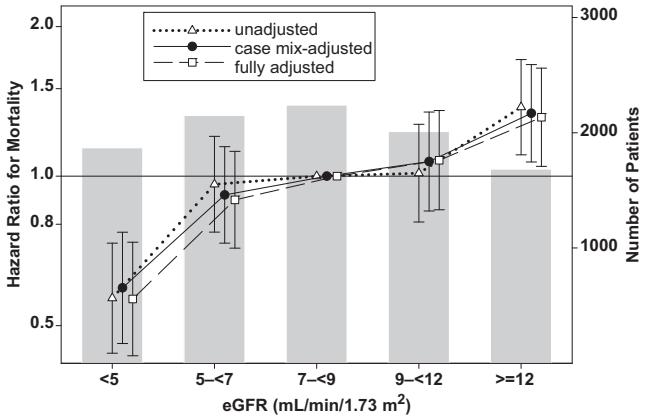

Figure 3. Hazard ratios for mortality across estimated glomerular filtration rates (eGFRs) at dialysis therapy initiation.

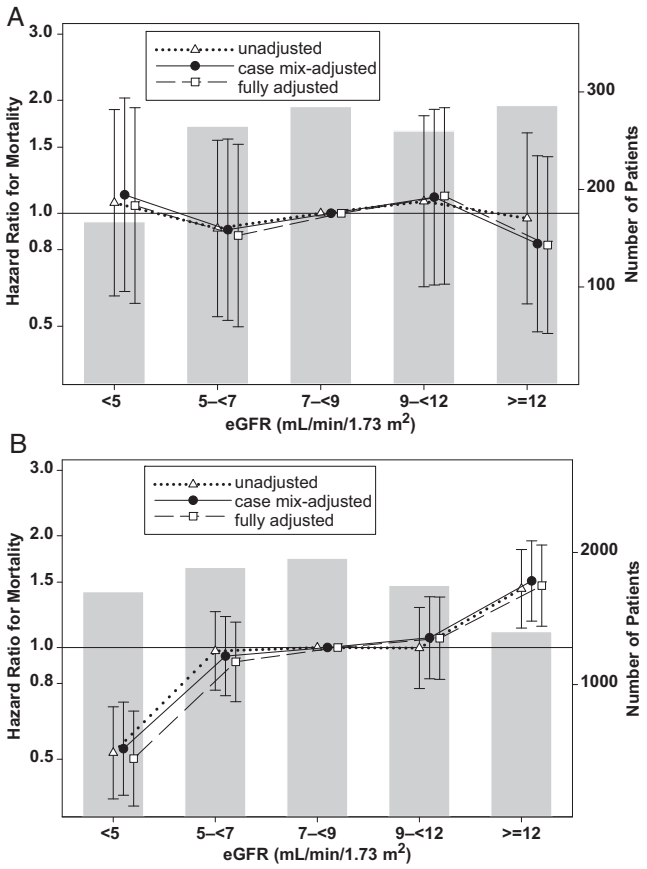

Figure 4. Hazard ratios for mortality in patients (A) younger than 6 years and (B) 6 years or older. Abbreviation: eGFR, estimated glomerular filtration rate.

level, which are representative markers of nutritional status in children.[33,34] However, we were unable to fully account for nutritional status, including information on dietary intake and normalized protein catabolic rate. Nutritional status influences not only mortality but also growth, which is one of the main outcomes investigated in children treated by dialysis,[35] and further studies are needed to examine the association of eGFR with mortality, including more meticulous nutritional assessment. Because younger patients need complicated and specific management due to technical difficulties for vascular access, have a high risk for mortality, have a high risk for growth failure, and have a high nutritional requirement,[36-39] we focused on patients aged 1 to younger than 6 years in our subgroup analysis. In our study, there was no difference in mortality risk across eGFRs in this age range. However, it should be noted that the sample size was small and larger studies are needed to further investigate these patients.

Our results indicate that patient characteristics such as age, sex, race, ethnicity, comorbid conditions, and hemoglobin level could be predictors of eGFR at dialysis therapy initiation. However, among these characteristics, there may be reverse causation between hemoglobin level and eGFR. Because of the high risk for anemia with advancing CKD stage,[40,41] dialysis therapy initiation at lower eGFRs might be a cause of lower hemoglobin levels due to longer time exposure to CKD stage 5 before entry into our study. Comorbid conditions have also been associated with higher mortality risk in children on dialysis therapy.[42,43] All comorbid conditions used in our analysis, that is, hypertension, heart disease, nonrenal anomaly, malignancy, and diabetes, were not effect modifiers according to interaction tests, and in subgroup analysis, our results showed consistent association in strata for all comorbid conditions. However, the numbers of patients who had comorbid conditions were small. Previous studies have showed inverse results for age[15] and sex[15,17] compared to our study. Particularly, Seikaly et al reported that female patients were more likely to start dialysis therapy with eGFRs < 5 mL/min/1.73 m^2 as compared to male patients, although they used a similar cohort to ours, that is, a cohort of 4,808 children starting dialysis therapy between 1995 and 2002 in the USRDS.[17] This discrepancy may be due to the formula used to calculate eGFR.[15] The original Schwartz formula[20] used in Seikaly et al[17] has several different equations based on age and sex to calculate eGFR, whereas we used the 2009 Schwartz formula in our primary analysis, which has a single equation regardless of age and sex. The results of our sensitivity analysis, however, using the original Schwartz formula was consistent with that of Seikaly et al,[17] whereas an inverse association was observed using the 2009 Schwartz formula in the same cohort. This suggests that differences in these formulas need to be considered when examining eGFR and dialysis therapy timing in children.

An important limitation of the present study is the change in methods for Scr measurement and in the eGFR formula during the follow-up period. Before 2009, the original Schwartz formula based on Scr level measured using a Jaffé method was primarily used to calculate eGFR. In 2009, the new Schwartz formula was developed based on an enzymatic method. Meanwhile, the methods used for Scr measurement gradually changed from a Jaffé to an

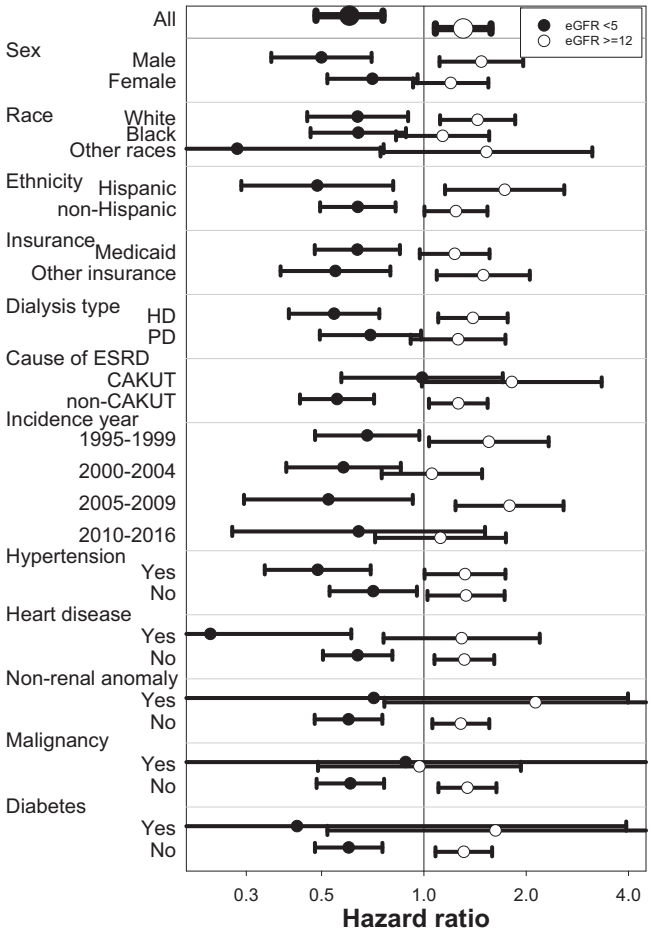

Figure 5. Case-mix–adjusted hazard ratios (HRs) in subgroup analyses by case-mix variables (reference: estimated glomerular filtration rate [eGFR], 5 to <12 mL/min/1.73 m^2). Lower limits of 95% confidence interval (CI) for other races (HR, 0.27; 95% CI, 0.10-0.70), heart disease (HR, 0.24; 95% CI, 0.09-0.61), nonrenal anomaly (HR, 0.71; 95% CI, 0.13-3.98), malignancy (HR, 0.88; 95% CI, 0.10-7.70), and diabetes (HR, 0.42; 95% CI, 0.05-3.94) for eGFRs < 5 mL/min/1.73 m^2 , and upper limits of 95% CI for nonrenal anomaly (HR, 2.13; 95% CI, 0.77-5.93) and diabetes (HR, 1.62; 95% CI, 0.52-5.07) for eGFRs ≥ 12 mL/min/1.73 m^2 are out of the graph. Abbreviations: CAKUT, congenital anomaly of the kidney and urinary tract; HD, hemodialysis; PD, peritoneal dialysis.

enzymatic method.[44] Although a Jaffé method was commonly used before 2005,[21] we did not have information on the method for Scr measurement in the USRDS and thus for all patients used the 2009 Schwartz formula, which is now widely used in clinical practice.[45] Even a small bias in Scr concentration could be a major concern in the assessment of kidney function due to lower Scr levels in children compared with adults.[46] Thus, the bias derived from the differences in creatinine assays might influence eGFR values calculated using the Schwartz formula in our cohort. However, given that the bias between the Jaffé and enzymatic method is 0.2 to 0.3 mg/dL[47,48] or 10%,[49] and the median Scr level of our cohort was 7.8 mg/dL, eGFRs calculated using the 2009 Schwartz formula using enzymatic Scr would likely be similar to that of the Jaffé Scr level.[49] For example, in a patient with a Scr level of 5.0 mg/dL and height of 100 cm, the eGFRs are 8.6 and 8.3 mL/min/1.73 m^2 if Scr was measured using the Jaffé and enzymatic methods, respectively.

Another way to address this difference in Scr measurement was to take into account the use of the Jaffé method by calculating eGFR using the original Schwartz formula. Thus, we performed sensitivity analyses using the original Schwartz formula in a cohort of incident patients between 1995 and 2004 in which a Jaffé method was the predominant method to measure Scr.[21] As indicated by the difference in results between Seikaly et al and our study, the changes in the Schwartz formula may influence observed results. However, sensitivity analysis for the main result showed a consistent association between eGFR and mortality. For secular trends, the degree of decrease in median Scr level from 8.9 mg/dL in 1995 to 1999 to 6.3 mg/dL in 2000 to 2016 was much larger than the bias between the Jaffé and enzymatic methods. Thus, an increasing trend in eGFRs at dialysis therapy initiation was observed regardless of methods for Scr measurement.

Technically, applying the 2009 Schwartz formula to our cohort may not be appropriate because it was originally developed using a cohort of patients aged 1 to 16 years and whose GFRs were in the range of approximately 15 to 75 mL/min/1.73 m^2. However, there are currently no estimating methods aside from the Schwartz formula for patients 17 years old and with eGFRs < 15 mL/min/1.73 m^2, and the Schwartz formula is widely used for these patients until dialysis therapy initiation in current clinical practice. Therefore, in keeping with clinical practice, we used the 2009 Schwartz formula despite this potential limitation.

Several other limitations should be acknowledged. First, we do not have information for patients who died before the transition to dialysis therapy, which may result in potential survivor bias, in that those who are able to transition may be stronger than those who did not.

There may also be potential selection bias. Compared with the 3,209 excluded patients, included patients were more likely to start dialysis therapy with hemodialysis and have lower BMI and greater serum albumin levels, but there were no remarkable differences in other patient characteristics (Table S4). Another important potential bias is lead-time bias because all patients were followed from the date of dialysis therapy initiation. Therefore, the mortality risk associated with higher eGFRs (earlier start) might be underestimated due to earlier dialysis therapy initiation compared with lower eGFRs. In consideration of our findings that dialysis initiaton with a higher eGFR is associated with a higher mortality risk, the overall results would not change even if a lead-time bias was excluded.

Second, subgroup analyses by age had limited statistical power due to small sample size. Although age is a potential effect modifier according to interaction tests, a larger sample

size is needed to better examine the association between eGFR and mortality in patients younger than 6 years.

Third, due to the nature of the observational study design, we could not make definitive statements about the causal associations between eGFR and mortality. We were also not able to exclude the possibility of residual confounding and the presence of unmeasured confounders, including urine volume, normalized protein catabolic rate, serum urea nitrogen level, and electrolyte and acid-base status, due to unavailability of these data in the USRDS.

In conclusion, we observed an incremental and linear association between eGFRs at dialysis therapy initiation and mortality, such that higher eGFRs at dialysis therapy initiation were associated with higher risk for mortality. Further studies are needed to elucidate the association between eGFR and mortality, especially among patients younger than 6 years. Moreover, additional studies are needed to evaluate the benefit of dialysis therapy initiation at lower eGFRs in children. Other relevant outcomes, including cardiovascular complications, access to transplantation, and growth, should also be examined.

Supplementary Material

Figure S1: HRs for mortality with restricted cubic spline in unadjusted, case mix–adjusted, and fully adjusted models.

Figure S2: HRs for mortality in 4,764 patients who started dialysis between 1995 and 2004.

Table S1: Secular trends in eGFR, Scr, and height at dialysis initiation.

Table S2: Likelihood of eGFR <5 and ≥12 mL/min/1.73 m^2 at dialysis initiation in 4,764 patients who started dialysis between 1995 and 2004.

Table S3: Cause of death according to age and eGFR.

Table S4: Comparison of included and excluded patients for characteristics.

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Support: The authors are supported by research grants from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases including T32-DK104687 (Dr Laster), K23-DK102903 (Dr Rhee), R03-DK114642 (Dr Rhee), K24-DK091419 (Dr Kalantar-Zadeh), and U01-DK102163 (Dr Kalantar-Zadeh), and philanthropist grants from H. Simmons, L. Chang, and J. Lee. Dr Tang is supported by the grant from Shengjing Hospital of China Medical University. The funders had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Financial Disclosure: Dr Kalantar-Zadeh has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO Oncology, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, International Federation of Kidney Foundations, International Society of Hemodialysis, International Society of Renal Nutrition and Metabolism, Japanese Society of Dialysis Therapy, Hospira, Kabi, Keryx, Novartis, National Institutes of Health, National Kidney Foundation, OPKO, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZSPharma. The other authors declare that they have no other relevant financial interests.

Disclaimer: The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government.

Peer Review: Received September 18, 2018. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an International Editor, and the Editor-in-Chief. Accepted in revised form December 17, 2018.

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