Sex and Glomerular Filtration Rate Trajectories in Children

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Abstract

Background and objectives Differences in CKD progression by sex have been hypothesized to explain disparities in access to kidney transplantation in children. This study aims to identify distinct trajectories of eGFR decline and to investigate the association of sex with eGFR decline.

Design, setting, participants, & measurements We used data from the CKD in Children study. Latent class mixed models were used to identify eGFR trajectories and patient characteristics were compared between trajectories. Progression was studied to two outcomes: ESKD (dialysis or transplantation) and a combined outcome of ESKD or 50% eGFR decline from baseline, using multivariable parametric failure time models.

Results Among 888 patients, 613 with nonglomerular and 275 with glomerular diseases, we observed four and two distinct GFR trajectories, respectively. Among patients with nonglomerular diseases, there was a higher proportion of males in the group with a low baseline GFR. This group had an increased risk of ESKD or 50% GFR decline, despite a similar absolute decline in GFR. Eight patients with nonglomerular diseases, mostly males with obstructive uropathies, had a more rapid absolute GFR decline. However, the association between male sex and rapid absolute GFR decline was NS after adjustment for age, baseline GFR, and proteinuria. Among patients with glomerular diseases, a subgroup including mostly females with systemic immunologic diseases or crescentic GN had a rapid absolute GFR decline.

Conclusions This study identifies different trajectories of CKD progression in children and found a faster progression of CKD in females in patients with glomerular diseases, but no significant sex difference in patients with nonglomerular diseases. The differences in progression seem likely explained by sex differences in the underlying primary kidney disease and in baseline GFR rather than by a direct effect of sex on progression.

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Introduction

CKD affects 15% of the adult population in the United States (1). The prevalence of CKD in children is much lower. Several European studies estimated this prevalence to be between 55 and 95 patients per million children (2–5), representing around 0.01% of children; however, surveillance studies in the general population suggest a much higher prevalence of approximately 1% (6,7). CKD is associated with many complications, including poor growth, metabolic bone disease, and anemia (8). Moreover, progression to ESKD compromises the life expectancy of these children, with an age-specific mortality rate for children receiving dialysis that is 30 times higher than in healthy children (9). Many studies aimed to identify risk factors for CKD progression and focused on modifiable risk factors such as hypertension (10), proteinuria (10), acidosis (11), and elevated uric acid levels (12), with the ultimate goal to design interventions to slow CKD progression. Fewer studies reported on nonmodifiable risk factors. However, both modifiable and nonmodifiable risk factors can be used to identify patients at high risk of progression to ESKD and to better prepare these patients for dialysis and transplantation.

The prevalence and incidence of CKD and ESKD are higher in men (13,14) and boys (15), compared with women and girls. In adults, male sex is associated with a faster CKD progression, even when comparing patients with the same underlying disease (16). This observation was strengthened by animal studies suggesting that estrogens may slow progression (17) and clinical studies supporting their protective effects against kidney injury (18).

Among children, females have been reported to have delayed access to transplantation and lower access to preemptive transplant. A recent study from the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) registry suggested that a faster CKD progression in females than in males might partially explain these disparities (19).

Finally, many studies investigating CKD progression used ESKD, or a combination of rate of GFR decline and ESKD, as the primary outcome. However, these

outcomes may not reflect the true progression rate of CKD because they are highly dependent on the baseline GFR and differences in medical practice on when to initiate KRT (20).

In this study, we used recently developed statistical methodologies to investigate the trajectories of GFR decline in children with CKD and whether differences in CKD progression exist between males and females.

Materials and Methods

Study Population

The CKD in Children (CKiD) study design, methods, and baseline characteristics of the cohort have been described previously (21,22). Patients 1–16 years of age with an eGFR of 30–90 ml/min per 1.73 m^2 were enrolled from 54 participating centers in the United States, from January 2005 to July 2009. In this longitudinal observational cohort study, we used the data from the CKiD study publicly available through the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository. The study was approved by the ethics committee of our institution.

Data Collected

Patient Data. Patient data included demographics; clinical characteristics, including primary CKD diagnosis and type of disease (glomerular or nonglomerular); pubertal status, categorized using the Tanner classification based on testicular volume in males and breast development in females; and comorbidities at the time of inclusion (diabetes, hypertension, and history of febrile urinary tract infection [UTI]). We also collected laboratory values at baseline, including urine protein/creatinine (Up/c) ratio, serum albumin, acidosis, uric acid, serum potassium, phosphate, and anemia defined as a hemoglobin less than fifth percentile using age- and sex-specific norms (23).

Measurements of Glomerular Filtration Rate. The eGFR was estimated using the modified Schwartz equation based on centrally measured serum creatinine, cystatin C, and BUN using the updated Schwartz formula (24).

Statistical Analysis

To identify subgroups of distinct eGFR trajectories over time, we used latent class linear mixed model (LCMM). LCMM is an extension of the standard linear mixed model that takes into account the expected heterogeneity among the eGFR trajectories in patients with various types of primary kidney diseases. It is made of two joint submodels: (*1*) a linear mixed model specific to each latent class where the observed eGFR value of each patient at a specific time point is expressed as the sum of the expected value of eGFR at that time and the individual patient's departure from that expected value of eGFR, and (*2*) a multinomial logistic regression model that expressed the probability for each patient of belonging to each subgroup of trajectories (25,26). We used the quadratic function of time to model eGFR trajectories to allow for nonlinear trajectories. This model does not require the same number of eGFR measures per patient, or that these measures are taken regularly or at the same time points for all patients (25), and accounts for patients with only one eGFR measure to reduce selection bias (27). A detailed description of model fit and accuracy is provided in the Supplemental Methods and Supplemental Tables 1 and 2. Patient characteristics are presented as medians and interquartile ranges (IQR) for continuous variables, and counts and percentages for categoric variables. Chi-squared test or Fisher exact test and ANOVA were used to compare patient characteristics at baseline between sex and eGFR trajectory groups for categoric variables and continuous variables, respectively, and multivariable logistic regression models were used to assess characteristics independently associated with each trajectory. To compare our results to previous reports on CKD progression (28), we studied progression to two commonly used outcomes: ESKD (defined as maintenance dialysis or transplantation) and a combined outcome of ESKD or 50% eGFR decline from baseline. Multivariable parametric failure time models assuming a log-normal distribution of failure times were used to evaluate the association between eGFR trajectories and outcomes. This method was chosen for comparison purposes with a previously published study on the CKiD data and because it provides a clinically relevant way to communicate the results in terms of relative time rather than hazard ratios. We also performed a sensitivity analysis excluding patients with only one eGFR assessment. Statistical analyses were performed using SAS 9.4 for Windows (SAS Institute) and R statistical software version 3.6.1 (R Foundation for Statistical Computing). The "lcmm" R package (29) was used to fit LCMM models and a P value <0.05 was considered statistically significant.

Results

A total of 3931 eGFR assessments were available from 891 patients. We excluded 13 potentially incorrect eGFR values that resulted in the exclusion of three patients. A total of 888 patients were included: 549 males (62%) and 339 females (38%). They underwent 3941 visits and 3917 eGFR assessments over a median follow-up of 4.1 (IQR, 2.3–7.5) years (Figure 1). The median baseline age was 11 (IQR, 8–15) years, and 613 (69%) had a nonglomerular disease. Table 1 presents the demographic and clinical characteristics of our study population overall and by sex (Supplemental Table 3). Males tended to be younger, had a lower baseline eGFR, and had more nonglomerular diseases than females. They also had a higher prevalence of CKD complications such as anemia and elevated phosphate levels.

Analysis of Estimated Glomerular Filtration Rate Trajectories

When studying the whole cohort, the best model included five latent trajectories defining five groups with similar eGFR trajectories (Figure 2A). Three groups had a slow and linear eGFR decline and differed only by their baseline eGFR; they accounted for the majority of our patients (784/888, 88%). Patients in the two other groups had a relatively high baseline eGFR and experienced a faster decline, with either a linear decline or a polynomial decline.

Because the type of underlying primary kidney disease is a major predictor of CKD progression in children, we decided to further stratify the study of the eGFR trajectories by type of primary kidney disease, differentiating between

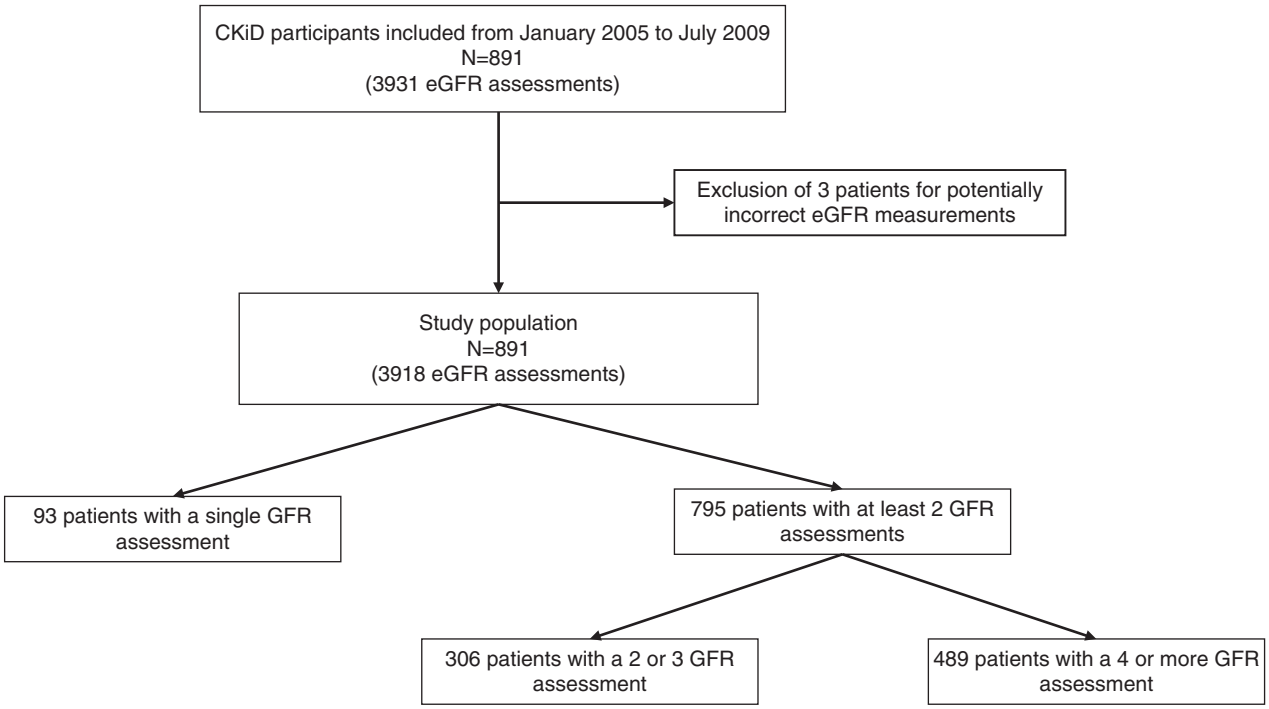

Figure 1. | **Flowchart of patients' visits and eGFR assessments.** CKiD, CKD in Children.

glomerular versus nonglomerular diseases. Among patients with glomerular primary kidney diseases, we observed two eGFR trajectories. There were 52 patients with a rapid eGFR decline and 223 patients with a moderate eGFR decline (Figure 2B). Among patients with nonglomerular primary kidney diseases, we observed four eGFR trajectories (Figure 2C). One had a slow and linear eGFR decline with a moderately impaired baseline eGFR (206 patients), two had a moderate and linear decline of eGFR and only differed by their baseline eGFR (high baseline eGFR, 216 patients; low baseline eGFR, 183 patients). There were only eight patients that had a moderately impaired baseline eGFR, followed by a rapid decline. The individual trajectories by group are presented in Supplemental Figures 1, 2 and 3 for all patients, patients with glomerular diseases, and patients with nonglomerular diseases, respectively. Because most patients with nonglomerular diseases can be assumed to have CKD since birth, we repeated the study of eGFR trajectories in this subgroup with a chronologic age timescale. Overall, we observed the same four eGFR trajectories (Supplemental Figure 4), but some patients changed assigned trajectory, with 14, 412, and 187 patients classified as having fast, moderate, and slow progression, respectively.

Demographic and Clinical Factors Associated with CKD Progression

Patients' characteristics associated with eGFR trajectories are presented in Table 2 and Table 3 for non-glomerular and glomerular patients, respectively. Among patients with nonglomerular diseases, patients with low eGFR/moderate eGFR decline or fast eGFR decline were more likely to be males, had a higher Up/c ratio, and lower serum albumin levels (Table 2). Patients in the group with low baseline eGFR were more likely to have abnormalities related to low eGFR, including anemia, hyperphosphatemia, and acidosis. Patients with a fast decline tended to be younger and were significantly more likely to have a history of recurrent UTIs and half of the patients had obstructive uropathy, most commonly posterior ureteral valves. The distribution of primary kidney diseases was similar between patients with slow or moderate eGFR decline (Supplemental Tables 2 and 3). Pubertal status was not associated with eGFR trajectory, even after adjusting for age and sex ($P=0.90$). Moreover, the effect of pubertal status was not different between males and females (interaction term nonsignificant, $P=0.76$). When performing the multivariable analysis, the two trajectories with a moderate absolute eGFR decline were grouped and formed a group of 399 patients. After adjusting for age, baseline eGFR, and proteinuria, sex was not significantly associated with trajectories of eGFR decline among patients with nonglomerular diseases (Table 4). Moreover, the association between sex and eGFR trajectories was further attenuated when using chronologic age as the timescale, with females accounting for 36% of patients in the fast eGFR decline group, which is similar to 33% and 37% in the moderate and slow eGFR decline groups, respectively. The multivariate analysis similarly found an absence of association between sex and eGFR decline: odds ratios for males versus females to belong to the moderate or fast eGFR decline groups (versus slow decline) were 1.04 (95% confidence interval [95% CI], 0.85 to 1.26) and 0.97 (95% CI, 0.55 to 1.73), respectively.

Among patients with glomerular diseases, patients with rapid eGFR decline were more likely to be females and had a higher prevalence of hypoalbuminemia (Tables 3 and 4).

Table 1. Demographics and clinical characteristics of the patients from the CKD in Children study at inclusion in the cohort by sex (inclusion between 2005 and 2009)

Baseline Characteristics	All Cohort (n=888)	Male (n=549)	Female (n=339)
Age, median (IQR)	11 (8–15)	11 (7–15)	12 (8–15)
Race, *n* (%)			
White	608 (68)	366 (67)	242 (71)
Black	197 (22)	133 (24)	64 (19)
Other	83 (9)	50 (9)	33 (10)
Puberty, *n* (%)	401 (45)	219 (40)	182 (54)
Primary kidney disease, *n* (%)			
Glomerular disease	275 (31)	147 (28)	128 (38)
Nonglomerular disease	613 (69)	402 (73)	211 (62)
Hypertension, *n* (%)	415 (47)	247 (45)	168 (50)
Diabetes, *n* (%)	9 (1)	5 (1)	4 (1)
History of febrile UTI, *n* (%)	258 (29)	157 (29)	101 (30)
Baseline GFR, median (IQR)	53 (39–68)	52 (36–67)	54 (41–70)
Urine protein-creatinine ratio, *n* (%)			
<0.5	335 (38)	205 (37)	130 (38)
0.5–2	155 (17)	92 (17)	63 (19)
≥2	89 (10)	59 (11)	30 (9)
Low serum albumin, *n* (%)	85 (10)	48 (9)	37 (11)
High potassium (>5.2 mEq/L), *n* (%)	68 (8)	42 (8)	26 (8)
Acidosis (CO_2<22 mEq/L), *n* (%)	458 (52)	271 (49)	187 (55)
High phosphate, *n* (%)	133 (15)	98 (18)	35 (10)
Uric acid, *n* (%)			
Low (<5.5)	122 (14)	73 (13)	48 (14)
Moderate (5.5–7.5)	152 (17)	92 (17)	60 (18)
High (>7.5)	51 (6)	36 (7)	15 (4)
Anemia, *n* (%)	265 (30)	182 (33)	83 (24)

Missing: puberty, n=50; hypertension, n=16; diabetes, n=5; history of febrile UTI, n=52; urine protein-creatinine ratio, n=309; serum albumin, n=8; potassium, n=19; acidosis, n=8; phosphate, n=2; uric acid, n=564; anemia n=21. IQR, interquartile range; UTI, urinary tract infection; CO_2, carbon dioxide.

The distribution of the primary kidney diseases differed between the two groups, with a higher prevalence of systemic immunologic diseases (including lupus nephritis) and idiopathic crescentic GN in rapid progressors. In the group with moderate eGFR decline, FSGS was the leading primary kidney disease (Supplemental Tables 5 and 6).

Estimated Glomerular Filtration Rate Trajectories and ESKD

We assessed the association between the eGFR trajectories and the two outcomes classically used to study CKD progression: (*1*) ESKD alone, and (*2*) the combined outcome of ESKD or 50% eGFR decline from baseline (progression-free survival). Figure 3A presents progression-free survival and Figure 3B presents ESKD-free survival by CKD trajectory among patients with nonglomerular disease. Among patients with moderate absolute rates of eGFR decline, patients with low baseline eGFR had a higher risk of meeting the outcomes compared with patients with moderately impaired baseline eGFR, despite similar absolute rates of eGFR decline. In contrast, patients with a moderately impaired baseline eGFR and either a rapid decline or a moderate eGFR decline had a higher risk of ESKD or the combined outcome, despite a higher baseline eGFR due to their faster eGFR decline. To quantify differences in the rates of progression between the groups, relative time to outcome were estimated. A relative time below one means a faster progression; a group with a relative time of 0.5 reaches the outcome twice as fast as the reference group. When compared with patients with moderately impaired baseline eGFR and slow eGFR decline, patients with low baseline eGFR/moderate eGFR decline, moderately impaired baseline eGFR/rapid eGFR decline, and moderately impaired baseline eGFR/moderate eGFR decline had a relative time to ESKD or 50% eGFR decline of 0.25 (95% CI, 0.20 to 0.32), 0.14 (95% CI, 0.07 to 0.25), and 0.54 (95% CI, 0.43 to 0.69), respectively.

Figure 3C presents progression-free survival and Figure 3D presents ESKD-free survival by CKD trajectory among patients with glomerular disease. When compared with patients with moderate eGFR decline, patients with rapid eGFR decline had a relative time to ESKD or 50% eGFR decline of 0.73 (95% CI, 0.41 to 1.31).

We performed a sensitivity analysis excluding patients with only one eGFR assessment. Overall, excluding these patients did not significantly change the results.

Discussion

In this study, we explored CKD progression by reporting the eGFR trajectories of pediatric patients included in the CKiD study. Along with the previously reported faster progression of patients with glomerular diseases (30), we observed two and four distinct eGFR trajectories among patients with glomerular and nonglomerular diseases, respectively. Among patients with nonglomerular diseases, it appears to be a higher proportion of males in the group with a low baseline eGFR. This group had an increased risk of KRT or 50% eGFR decline despite a low absolute decline in eGFR. Eight patients with nonglomerular diseases,

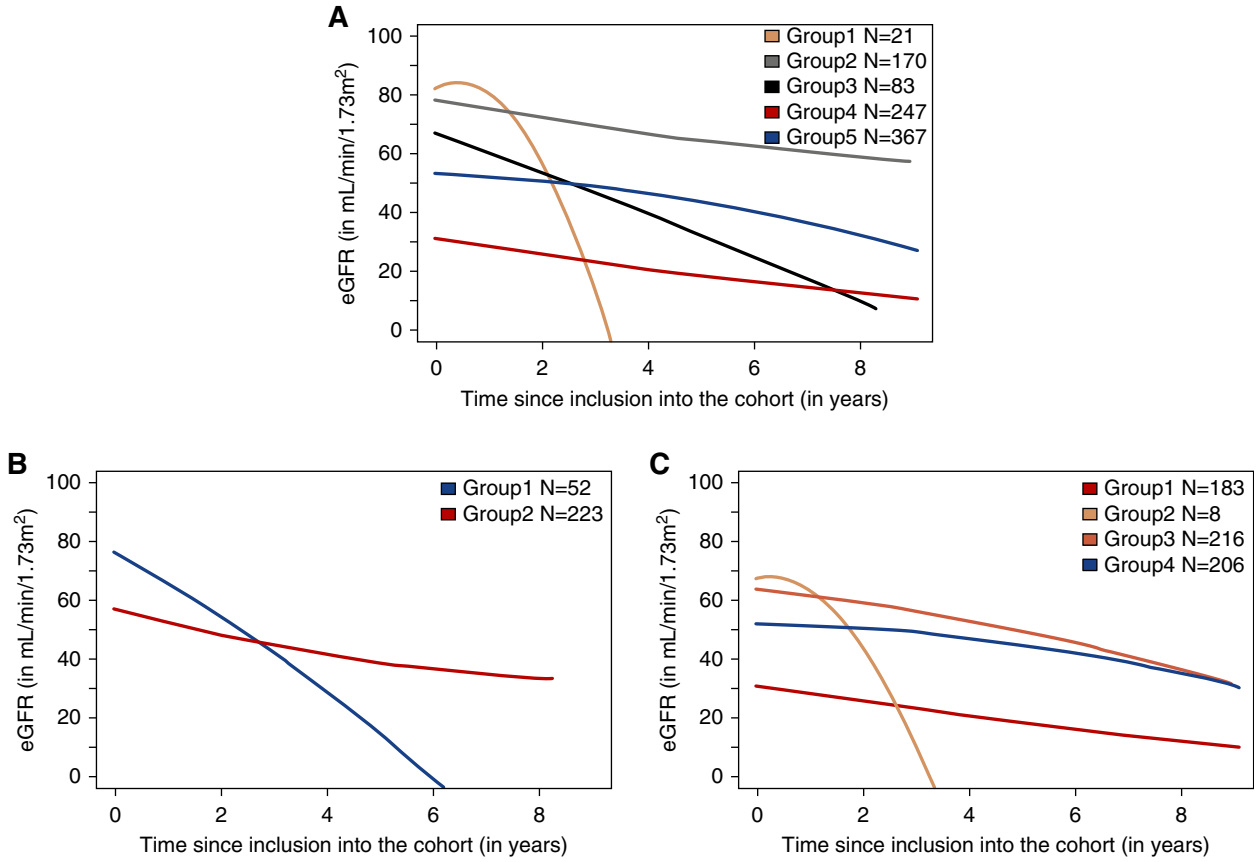

Figure 2. | **Latent trajectories of eGFR in the CKiD cohort; in all patients and in patients with glomerular and nonglomerular diseases.** (A) All patients: group 1 (high baseline eGFR, rapid nonlinear decline), group 2 (high baseline eGFR, slow decline), group 3 (high baseline eGFR, rapid linear decline), group 4 (low baseline eGFR, slow decline), and group 5 (moderately impaired baseline eGFR, slow decline). (B) Patients with glomerular diseases: group 1 (rapid eGFR decline), group 2 (moderate eGFR decline). (C) Patients with nonglomerular diseases: group 1 (low baseline eGFR, moderate decline), group 2 (high baseline eGFR, rapid decline), group 3 (high baseline eGFR, moderate decline), and group 4 (moderately impaired baseline eGFR, slow decline).

mostly males with obstructive uropathies due to posterior ureteral valves, had a more rapid absolute eGFR decline. However, the association between male sex and rapid absolute eGFR decline was attenuated after adjustment for age, baseline eGFR, and proteinuria, and was not observed when using chronologic age as the timescale. Among patients with glomerular diseases, a subgroup of patients, mostly females with systemic immunologic diseases or crescentic GN, had a rapid absolute eGFR decline. Consistent with previous studies, elevated proteinuria was associated with a faster progression and lower eGFR (31). Acidosis, anemia, and hyperphosphatemia were associated with a lower baseline eGFR. Overall, CKD progression in children seems to be mostly dependent on the underlying primary kidney disease that defines both the baseline eGFR and the absolute eGFR loss.

In adults, men have faster CKD progression, even when comparing patients with the same underlying disease such as diabetic nephropathy (17). Conversely, there is sex inequity in access to kidney transplantation waiting lists, with women having less access than men (32–34). Factors contributing to these differences include a longer transplantation workup in women, potentially resulting from a decreased willingness of women to undergo transplantation (35), as well as a higher level of donor-specific antibodies secondary to pregnancies. However, in children, the influence of such factors should be negligible. Nevertheless, Nguyen *et al.* (36) found that females in the United States have a 22% lower access to being waitlisted. This disparity in access to transplantation was recently confirmed in a study from the ERA-EDTA registry (19). The pretransplant workup to assess the suitability of a patient for transplant and gather the information needed to add him or her to the kidney waiting list takes time. This workup time adds to the total waiting time needed to receive a suitable kidney transplant offer. Therefore, starting this process early would allow earlier access to transplantation, but late diagnosis or fast eGFR decline can preclude timely access to kidney transplantation. The study from the ERA-EDTA registry also demonstrated that, despite similar eGFR at first appointment with a nephrologist and at KRT start, females tended to have a shorter interval from first appointment to initiation of KRT, suggesting a faster eGFR decline. However, pre-KRT eGFR data were only available in a subset of patients and eGFR decline was not stratified by type of primary kidney disease. In this pediatric study, we did not find a significant difference in absolute eGFR decline between males and females. In adults, differences in

Table 2. Baseline characteristics of patients with nonglomerular diseases by groups of GFR trajectory (inclusion between 2005 and 2009)

Baseline Characteristics	Slow Decline (n=206)	High Baseline eGFR/Moderate Decline (n=216)	Low Baseline eGFR/Moderate Decline (n=183)	Rapid Decline (n=8)
Age, median (IQR)	10.0 (6.0–13.0)	9.0 (5.5–13.0)	12.0 (8.0–15.0)	7.5 (3.0–12.0)
Female sex, *n* (%)	81 (39)	77 (36)	51 (28)	2 (25)
Race, *n* (%)				
White	159 (77)	157 (73)	138 (75)	5 (63)
Black	31 (15)	46 (21)	33 (18)	3 (37)
Other	16 (8)	13 (6)	12 (7)	0 (0)
Puberty, *n* (%)	76 (37)	60 (28)	82 (45)	2 (25)
Hypertension, *n* (%)	94 (46)	89 (41)	79 (43)	2 (25)
Diabetes, *n* (%)	1 (1)	1 (1)	0 (0)	0 (0)
History of febrile UTI, *n* (%)	75 (36)	73 (34)	76 (42)	6 (75)
Baseline GFR, median (IQR)	50.3 (45.1–56.0)	68.2 (58.5–79.7)	30.3 (25.3–35.3)	65.5 (54.4–95.6)
Urine protein-creatinine ratio, *n* (%)				
<0.5	89 (43)	126 (58)	25 (14)	4 (50)
0.5–2	25 (12)	19 (9)	46 (25)	0 (0)
≥2	9 (5)	12 (6)	31 (17)	1 (13)
Low serum albumin, *n* (%)	3 (1)	1 (0)	9 (5)	1(12)
High potassium (>5.2 mEq/L), *n* (%)	14 (7)	13 (6)	17 (9)	1 (13)
Acidosis (CO_2<22 mEq/L), *n* (%)	106 (51)	99 (46)	121 (66)	3 (37)
High phosphate, *n* (%)	15 (7)	13 (6)	42 (23)	0 (0)
Uric acid, *n* (%)				
Low (<5.5)	10 (5)	53 (25)	1 (1)	4 (50)
Moderate (5.5–7.5)	26 (13)	47 (22)	1 (1)	1 (13)
High (>7.5)	13 (6)	11 (5)	3 (2)	0 (0)
Anemia, *n* (%)	43 (21)	26 (12)	82 (45)	4 (50)

Missing: puberty, n=35; hypertension, n=9; diabetes, n=4; history of febrile UTI, n=39; urinary protein-creatinine ratio, n=226; serum albumin, n=4; potassium, n=14; acidosis, n=4; phosphate, n=1; uric acid, n=473; anemia, n=19. IQR, interquartile range; UTI, urinary tract infection; CO_2, carbon dioxide.

comorbidities or risk factors of CKD progression, such as smoking or hypertension, have been hypothesized to explain this sex difference. Experimental models on rats also suggested that hormonal factors may slow down kidney-function loss in women (17). However, endocrine factors may be less relevant in pediatric CKD, and we did not find differences in the association of sex with CKD progression in patients who were prepubertal versus postpubertal. Finally, the low prevalence in children of extrakidney comorbidities and other risk factors for progression may explain the absence of a significant difference in CKD progression between sexes in our study.

The results of the analysis using chronologic age as timescale, showing the disappearance of the trend between male sex and fast eGFR decline among patients with nonglomerular diseases, is also of interest because it suggests that failing to capture the complete eGFR trajectory of the patient might induce some selection bias (*i.e.*, males included earlier than females) that might not be fully accounted for when studying CKD progression.

This study is the first to our knowledge to use LCMM methodology to investigate CKD progression in children. The strength of this methodology is that it takes into account the baseline eGFR and the absolute decline in eGFR during the process of identifying subgroups of CKD progression. Indeed, most of the studies on CKD progression, including a previous one on the same cohort (28), used relative eGFR loss and ESKD as a primary outcome. However, ESKD occurrence heavily depends on baseline eGFR, which limits the use of "time to ESKD" as a reliable marker of CKD progression. Similarly, the use of a 50% eGFR decline is limited by the fact that similar absolute eGFR loss can cause very different relative eGFR loss depending on the baseline eGFR. These limitations can only partially be compensated for by adjustment on baseline eGFR or CKD stage and support the use of methods like the one used in this study which incorporate both baseline eGFR and absolute decline.

Finally, predicting CKD progression is a major challenge in nephrology. Especially in children, transplantation is the treatment of choice for ESKD because it is associated with better survival and improved quality of life compared with dialysis (37–39). Whenever possible, dialysis should be avoided by providing access to preemptive transplantation. More accurate predictions of the time to ESKD would potentially help clinicians better prepare patients for transplantation or create a vascular access for dialysis if needed. In a recent study based on the data from CKiD and ESCAPE, Furth *et al.* (40) published an update of the Kidney Disease Improving Global Outcomes guidelines

Table 3. Baseline characteristics of patients with glomerular diseases by groups of GFR trajectory (inclusion between 2005 and 2009)

Baseline Characteristics	Rapid Decline (n=52)	Moderate Decline (n=223)
Age, median (IQR)	13.0 (9.0–15.0)	14 (11.0–16.0)
Female sex, *n* (%)	31 (60)	97 (44)
Race, *n* (%)		
White	30 (58)	119 (53)
Black	15 (29)	69 (31)
Others	7 (13)	35 (16)
Puberty, *n* (%)	31 (60)	150 (67)
Hypertension, *n* (%)	26 (50)	125 (56.1)
Diabetes, *n* (%)	2 (4)	5 (2)
History of febrile UTI, *n* (%)	9 (17)	19 (9)
Baseline GFR, median (IQR)	93.8 (71.8–107.6)	54.9 (39.2–72.5)
Urine protein-creatinine ratio, *n* (%)		
<0.5	23 (44)	68 (31)
0.5–2	11 (21)	54 (24)
≥2	7 (14)	29 (13)
Low serum albumin, *n* (%)	17 (33)	54 (24)
Elevated potassium (>5.2 mEq/L), *n* (%)	7 (14)	16 (7)
Acidosis (CO_2<22 mEq/L), *n* (%)	23 (44)	106 (48)
High phosphate, *n* (%)	11 (21)	52 (23)
Uric acid, *n* (%)		
Low (<5.5)	19 (37)	34 (15)
Moderate (5.5–7.5)	12 (23)	65 (29)
High (>7.5)	2 (4)	22 (10)
Anemia, *n* (%)	21 (40)	89 (40)

Missing: hypertension, n=7; diabetes, n=1; history of febrile UTI, n=13; urinary protein-creatinine ratio, n=83; serum albumin, n=4; potassium, n=5; acidosis, n=4; phosphate, n=1; uric acid, n=121; anemia, n=2; puberty, n=15. IQR, interquartile range; UTI, urinary tract infection; CO_2, carbon dioxide.

aiming to predict the risk of CKD progression based on the type of primary kidney disease (glomerular versus nonglomerular), eGFR, and Up/c ratio. However, they used a combined outcome of 50% decline in eGFR or ESKD. Therefore, specific models predicting absolute outcome such as KRT initiation are needed (41). Recently, Winnicki *et al.* (42) assessed the accuracy of the Kidney Failure Risk Equation to predict progression to ESKD in children included in the CKiD study and reported that both the four-variables score (including age, sex, eGFR, and albumin-creatinine ratio) and the eight-variables score (with the addition of serum calcium, phosphate, bicarbonate, and albumin levels) yielded a very high accuracy, with *c*-statistics around 0.9 for 1-year prediction. In this study, sex remained an independent predictor of ESKD, however, our study suggests this may be due to differences in the distribution of primary kidney diseases between males and females. Thus, this risk score could be used to refer patients to pretransplant workup, and the inclusion of more precise categories of primary kidney disease instead of the classic glomerular and nonglomerular categories might further improve the prediction.

This study has several limitations. Although GFR was measured using iohexol disappearance in CKiD, we used

Table 4. Adjusted associations of clinical characteristics with eGFR trajectory groups in patients with glomerular and nonglomerular primary kidney diseases

Baseline Characteristics	Nonglomerular Diseases[a]		Glomerular Diseases[b]
	OR (95% CI) of Moderate eGFR Decline	OR (95% CI) of Rapid eGFR Decline	OR (95% CI) of Rapid eGFR Decline
Age (per 1-yr increase)	1.01 (0.97 to 1.05)	0.99 (0.82 to 1.20)	1.03 (0.93 to 1.15)
Male sex (versus female)	1.20 (1.00 to 1.44)	2.08 (0.70 to 6.20)	0.61 (0.41 to 0.92)
Baseline GFR (per 10 ml/min per 1.73 m^2 increase)	1.08 (0.97 to 1.18)	1.51 (1.10 to 1.92)	1.83 (1.60 to 2.10)
Urine protein-creatinine ratio			
<0.5	Reference	Reference	Reference
0.5–2	0.96 (0.62 to 1.48)	n/a	0.86 (0.42 to 1.78)
≥2	1.89 (1.09 to 3.28)	n/a	1.47 (0.56 to 3.87)

OR, odds ratio; n/a, not applicable.
[a]Reference group for nonglomerular diseases: slow eGFR decline group.
[b]Reference group for glomerular diseases: moderate eGFR decline group.

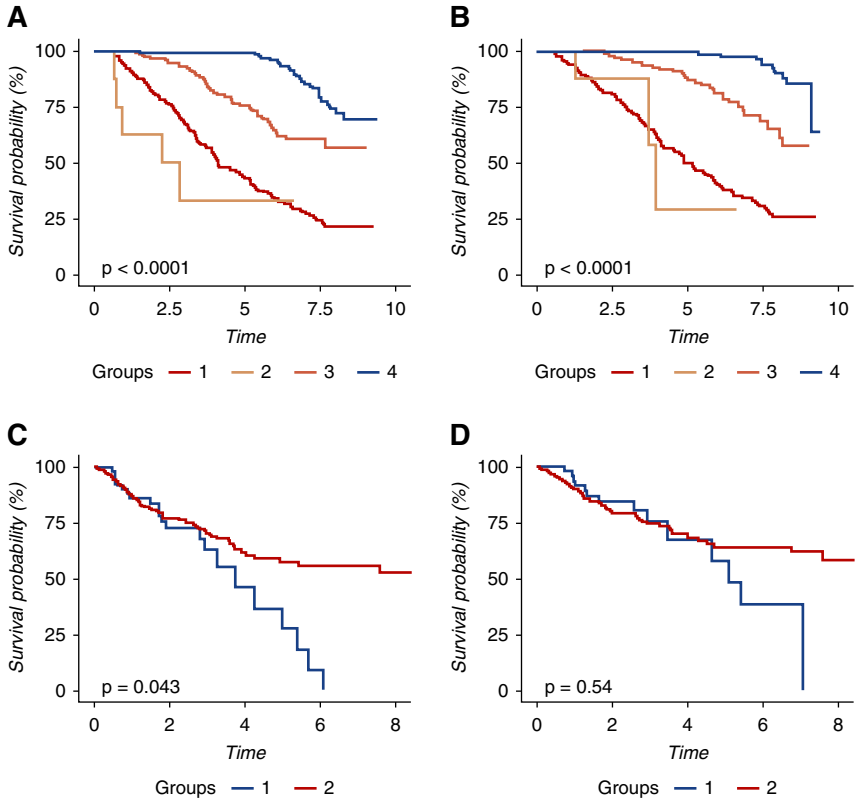

Figure 3. | **Progression-free survival by CKD trajectory among patients included in the CKiD cohort.** (A and C) Progression-free survival in (A) patients with nonglomerular and (C) patients with glomerular diseases. (B and D) ESKD-free survival in patients with (B) nonglomerular and (D) glomerular diseases. (A and B) Group 1 (low baseline eGFR, moderate decline), group 2 (high baseline eGFR, rapid decline), group 3 (high baseline eGFR, moderate decline), and group 4 (moderately impaired baseline eGFR, slow decline). (C and D) Group 1 (rapid eGFR decline) and group 2 (moderate eGFR decline).

eGFR based on the updated Schwartz formula to have as many eGFR assessments per patient as possible. There was some missing data for known risk factors of CKD progression. The potential effect of sexual hormones on CKD progression could only be extrapolated based on patients' clinical pubertal status at baseline, and we could not account for the effect of changes in pubertal status during follow-up. Finally, the method used also has some limitations. We used the quadratic function of time to model eGFR trajectories, and the shape of the latent trajectories was influenced by this assumption. Given the small sample sizes in some identified latent classes, our statistical power is limited to detect small differences between the groups and to detect interactions between risk factors. Finally, our study describes eGFR trajectories of pediatric patients with CKD and assigns each patient to a trajectory based on his or her observed eGFR values; further studies are needed to assess whether these trajectories can predict long-term CKD progression.

Nevertheless, the main strength of our study is the use of a large, prospective, and well described cohort of children with CKD with good quality eGFR estimation and repeated eGFR assessments, and the implementation of an innovative statistical methodology (LCMM) that does not rely on prior assumptions on the number of classes and the trajectories, allows modeling of baseline eGFR and eGFR decline together, and includes all available patients. This approach provides unique insights on the eGFR trajectories and the characteristics of the patients in each group.

In conclusion, we identified different trajectories of CKD progression in children. Although glomerular and nonglomerular diseases display very different trajectories, we found a faster progression in females among patients with glomerular diseases but only found a nonsignificant trend toward a faster progression of CKD in males with nonglomerular diseases. Differences in progression seem likely explained by sex differences in the underlying primary kidney disease and in baseline eGFR. Further studies are needed to explain the delayed access to transplantation in females. Our study also underlines the need to clearly differentiate absolute versus relative eGFR decline. Indeed, although studies investigating the pathophysiology and risk factors for eGFR decline should probably focus on absolute decline, predictive studies focusing on utility in clinical practice may favor relative decline, but should carefully choose their primary outcome based on their expected use in clinical practice.

Disclosures

Dr. Bonneric, Dr. Couchoud, Dr. Greenbaum, Dr. Hogan, Dr. Karadkhele, and Dr. Patzer have nothing to disclose.

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Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.08420719/-/DCSupplemental.

Supplemental Methods.

Supplemental Table 1. Posterior classification table of the final LCMM with 2 latent classes for glomerular patients.

Supplemental Table 2. Posterior classification table of the final LCMM with 4 latent classes for non-glomerular patients.

Supplemental Table 3. Demographics and clinical characteristics of the CKiD patients at inclusion in the cohort by sex and type of primary kidney disease.

Supplemental Table 4. Primary renal disease distribution by group of eGFR trajectory in non-glomerular patients. (A) Primary renal disease distribution by group of eGFR trajectory in non-glomerular patients after grouping the 2 trajectories with moderate absolute eGFR decline. (B) Primary renal disease distribution by group of eGFR trajectory in non-glomerular patients stratified by sex.

Supplemental Table 5. Primary renal disease distribution by group of eGFR trajectory in glomerular patients.

Supplemental Table 6. Primary renal disease distribution by group of eGFR trajectory in glomerular patients stratified by sex.

Supplemental Figure 1. Observed individual eGFR trajectories by latent class in all patients.

Supplemental Figure 2. Observed individual eGFR trajectories by latent class in patients with glomerular diseases.

Supplemental Figure 3. Observed individual eGFR trajectories by latent class in patients with non-glomerular diseases.

Supplemental Figure 4. Latent trajectories of GFR in non-glomerular patients using age as timescale.

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