Estimating Time to ESRD in Children With CKD

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Rationale & Objective: The KDIGO (Kidney Disease: Improving Global Outcomes) guideline for chronic kidney disease (CKD) presented an international classification system that ranks patients' risk for CKD progression. Few data for children informed guideline development.

Study Design: Observational cohort study.

Settings & Participants: Children aged 1 to 18 years enrolled in the North American Chronic Kidney Disease in Children (CKiD) cohort study and the European Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients (ESCAPE) trial.

Predictor: Level of estimated glomerular filtration rate (eGFR) and proteinuria (urine protein-creatinine ratio [UPCR]) at study entry.

Outcome: A composite event of renal replacement therapy, 50% reduction in eGFR, or eGFR < 15 mL/min/1.73 m^2. eGFR was estimated using the CKiD-derived "bedside" equation.

Analytical Approach: Accelerated failure time models of the composite outcome using a conventional generalized gamma distribution. Likelihood ratio statistics of nested models were used to amalgamate levels of similar risk.

Results: Among 1,232 children, median age was 12 (IQR, 8-15) years, median eGFR was 47 (IQR, 33-62) mL/min/1.73 m^2, 60% were males, and 13% had UPCRs > 2.0 mg/mg at study entry. 6 ordered stages with varying combinations of eGFR categories (60-89, 45-59, 30-44, and 15-29 mL/min/1.73 m^2) and UPCR categories (<0.5, 0.5-2.0, and >2.0 mg/mg) described the risk continuum. Median times to event ranged from longer than 10 years for eGFRs of 45 to 90 mL/min/1.73 m^2 and UPCRs < 0.5 mg/mg to 0.8 years for eGFRs of 15 to 30 mL/min/1.73 m^2 and UPCRs > 2 mg/mg. Children with glomerular disease were estimated to have a 43% shorter time to event than children with nonglomerular disease. Cross-validation demonstrated risk patterns that were consistent across the 10 subsample validation models.

Limitations: Observational study, used cross-validation rather than external validation.

Conclusions: CKD staged by level of eGFR and proteinuria characterizes the timeline of progression and can guide management strategies in children.

Complete author and article information (including a list of the CKiD and ESCAPE Study Investigators) provided before references.

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In adults and children, chronic kidney disease (CKD) is characterized by a progressive decline in kidney function to the point of failure.[1-3] Although CKD in children is uncommon,[4] it represents a higher cost per individual than adult CKD care.[2] The average life expectancy of pediatric patients with CKD initiating renal replacement therapy (RRT) in childhood in the United States is only 38 years for those receiving dialysis and 63 years for those with a kidney transplant.[4] To identify patients who are at highest risk for complications of kidney failure and other comorbid complications of CKD, a classification system has been developed by the KDIGO (Kidney Disease: Improving Global Outcomes) initiative based on 3 domains: cause of kidney disease, glomerular filtration rate (GFR) category, and albuminuria category.[5] The classification system ranks patients' risk for progression based on data derived from adults with CKD. These ordered categories have been promoted for use in clinical practice to predict the risk for adverse outcome and guide management strategies in adults with CKD. However, a similar system has not been validated for children with CKD.

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We used data collected from 2 large multicenter study consortia of children with CKD (the Chronic Kidney Disease in Children [CKiD] prospective cohort study[6] and the Effect of Strict Blood Pressure Control and ACE Inhibition on Chronic Renal Failure Progression in Pediatric Patients [ESCAPE] clinical trial[7]) to develop a modified KDIGO classification system for the pediatric CKD community. Classifying individuals by GFR, proteinuria (urine protein-creatinine ratio [UPCR]), and CKD diagnosis, we define unique stages of CKD progression risk. We also estimate progression timelines to help clinicians manage and plan future clinical care needs. We use cross-validation to explore the robustness of the classification system.

Methods

Study Participants and Design

Data in this analysis were pooled from CKiD and ESCAPE. CKiD is a prospective cohort study of children with CKD from 54 pediatric nephrology centers in North America who were aged 1 to 16 years with an estimated GFR (eGFR) of 30 to 90 mL/min/1.73 m^2. The study design and objectives have been previously reported.[6] ESCAPE is a randomized

trial at 33 pediatric nephrology centers in Western Europe in which 385 children 3 to 18 years of age with CKD (GFRs of 15-80 mL/min/1.73 m^2) received fixed-dose ramipril and were randomly assigned to intensified blood pressure control (with a target 24-hour mean arterial pressure < 50th percentile) or conventional blood pressure control. Patients were followed up to a 50% decline in GFR or progression to end-stage kidney disease.[7] Research protocols were approved by the institutional review boards at all participating sites and all participants gave written informed consent and/or assent. Analysis was restricted to children with baseline eGFRs > 15 mL/min/1.73 m^2, measured baseline UPCRs, and follow-up times greater than zero.

GFR and Biomarker Measurement

For all participants, GFR was estimated using the CKiD-derived and published "bedside" equation,[8] consistent with kidney function assessment in clinical practice.

In CKiD and ESCAPE, serum creatinine concentration was determined enzymatically. Proteinuria was defined using the first-morning UPCR.[9] All creatinine assays used isotope-dilution mass spectrometry–traceable standards.

Proteinuria rather than albuminuria was used in our assessment. Except in diabetes, tests for total urine protein are preferred in children. UPCR is a sensitive screening assay that is considered to be the standard for the measurement of proteinuria in children with CKD.[10]

CKD Progression Outcome Definition

The primary outcome of CKD progression was a composite end point defined as the earliest of either: (1) 50% reduction in baseline GFR, (2) eGFR < 15 mL/min/1.73 m^2, or (3) initiation of RRT (dialysis or transplantation).

Statistical Analysis

Demographic and clinical characteristics of the study population were summarized overall and by CKD diagnosis (glomerular vs nonglomerular CKD) using median and interquartile range (IQR) for continuous variables and percentage and frequency for categorical variables. Differences by diagnosis were tested using Wilcoxon rank sum tests for continuous variables and χ^2 tests for categorical variables. We categorized GFR as delineated by KDIGO[5]: ≥90 mL/min/1.73 m^2 (GI), 60 to 89 mL/min/1.73 m^2 (GII), 45 to 59 mL/min/1.73 m^2 (GIIIa), 30 44 mL/min/1.73 m^2 (GIIIb), and 15 to 29 mL/min/1.73 m^2 (GIV). We also modified the KDIGO guideline classification by using proteinuria rather than albuminuria: UPCR < 0.5 mg/mg, 0.5 to 2 mg/mg, and >2 mg/mg. Because there were few children with baseline GFRs ≥ 90 mL/min/1.73 m^2 and UPCRs ≥ 0.5 mg/mg, such children (n = 16) were reported in the study population description but excluded from the principal analysis.

Beginning with 13 unique GFR-UPCR levels (4 GFR by 3 UPCR categories, plus a category of GFR ≥ 90 mL/min/1.73 m^2 and UPCR < 0.5 mg/mg), we used a recursive amalgamation algorithm whereby GFR-UPCR levels with similar progression risks were combined iteratively.[11-13] Specifically, accelerated failure time models using a conventional generalized gamma distribution modeled the time from study baseline to the composite event within baseline GFR-UPCR levels, adjusting for CKD diagnosis and study cohort (CKID vs ESCAPE). Children who remained event free at the end of their follow-up were censored at the time of their last study visit. Likelihood ratio statistics of nested models were used to amalgamate GFR-UPCR levels of similar risk for the event. The process was repeated until no further amalgamation was warranted, as determined by the a priori statistical cutoff criterion of 0.01. This resulted in 6 CKD risk stages, labeled A (lowest risk) to F (highest risk). Robustness of the risk order and discriminating ability of the 6 risk stages for the outcome were evaluated in CKD-specific (glomerular vs nonglomerular) and cohort-specific (CKID vs ESCAPE) substrata of the study population using area under the receiver operating characteristic curve (AUROC).[14,15]

These final 6 risk stages were modeled with and without adjusting for diagnosis and cohort, as well as stratified by diagnosis to check for residual risk differences between diagnosis groups or study cohorts; the goodness-of-fit of these models were compared using Akaike information criteria. Parametrically estimated survival curves were compared using empirical Kaplan-Meier survival curves for the 6 risk groups, and diagnosis-specific event times for the 10th, 25th, and 50th percentiles of the study population were estimated.

The final model describing risk stages was validated using cross-validation methods[16] with the data divided into 10 random samples of 10% of the data.[17,18] Excluding each 10% sample in turn, parameters were estimated in the remaining 90% of data, yielding $\widehat{S}$ as the estimate of the survival function. For the 10% excluded, $w_i = -log\ \widehat{S}(t_i)$ should be a variate from the standard exponential distribution (ie, survival function = e^{-t}). Accurate model fit was assessed graphically by comparing the nonparametric Kaplan-Meier curve of the w_i from the 10 cross-validations and subjected to the same censoring of the original data against the survival function e^{-t} of the standard exponential.

Analyses were performed using SAS statistical software, version 9.3 (SAS Institute Inc), the survival ROC package in R 3.2.2 (R foundation for Statistical Computing), and S+ 8.2 for Windows (TIBCO Spotfire, Inc).

Results

Data were available for 1,269 children, 891 from CKiD and 378 from ESCAPE. Children missing baseline GFR or UPCR values (n = 26), having a baseline GFR < 15 mL/min/1.73 m^2 (n = 42), and having no follow-up data (n = 32) were excluded from analysis. Thus, analysis was restricted to 1,169 children, 857 from CKiD (73%) and 312 from ESCAPE (27%). Six CKiD children in this analysis died during study follow-up. Of those, 4 experienced an event before death; the other 2 were censored at their last CKID