Published in final edited form as:

Am J Kidney Dis. 2015 June ; 65(6): 878–888. doi:10.1053/j.ajkd.2015.01.008.

Predictors of Rapid Progression of Glomerular and Non-Glomerular Kidney Disease in Children: The CKiD Cohort

Bradley A. Warady, MD¹, Alison G. Abraham, MD², George J. Schwartz, MD³, Craig S. Wong, MD⁴, Alvaro Muñoz, PhD², Aisha Betoko, PhD², Mark Mitsnefes, MD, MS⁵, Frederick Kaskel, MD, PhD⁶, Larry A. Greenbaum, MD, PhD⁷, Robert H. Mak, MD, PhD⁸, Joseph Flynn, MD⁹, Marva M. Moxey-Mims, MD¹⁰, and Susan Furth, MD, PhD¹¹

¹Division of Pediatric Nephrology, Children's Mercy Hospital, Kansas City, MO

²Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

³University of Rochester, Rochester, NY

⁴University of New Mexico/Children's Hospital, Albuquerque, NM

⁵Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁶Children's Hospital at Montefiore, New York, NY

⁷Emory University and Children's Healthcare of Atlanta, Atlanta, GA

⁸University of California at San Diego, La Jolla, CA

⁹Seattle Children's Hospital, Seattle, WA

¹⁰National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

¹¹The Children's Hospital of Philadelphia, Philadelphia, PA

Abstract

Background—Few studies have prospectively evaluated the progression of chronic kidney disease (CKD) in children and factors associated with progression.

Study Design—Prospective assessment of risk factors for the composite event of renal replacement therapy (RRT) or 50% glomerular filtration rate (GFR) decline.

Address correspondence to: Bradley A. Warady, M.D., Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO 64108, Phone: 816-234-3812, Fax: 816-234-3494, bwarady@cmh.edu.

Contributions

The authors of the manuscript each contributed in a meaningful way. The specific contributions consisted of the following: research idea and study design: B.A.W., S.F., G.J.S., A.M.; data acquisition: A.M., A.B., A.G.A.; data analysis/interpretation: B.A.W., G.J.S., S.F., C.W., M.M., F.K., L.A.G., R.H.M., J.F., M.M.M.; statistical analysis: A.G.A., A.M. Each author contributed significant intellectual content during manuscript drafting and revision and accepts accountability for the overall work by assuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. B.A.W. takes responsibility that this study has been reported honestly, accurately and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Support and Financial Disclosure Declaration

The authors do not have any disclosures to report.

Setting and Participants—496 children with CKD enrolled in the Chronic Kidney Disease in Children (CKiD) study.

Outcomes—Parametric failure time models were used to characterize adjusted associations between baseline levels and changes of predictors and the time to composite event.

Results—The cohort consisted of 398 children with non-glomerular and 98 children with glomerular disease, of whom 29% and 41%, respectively progressed to the composite event after a median follow-up of 5.2 and 3.7 years. Demographic, clinical characteristics and outcomes differed substantially according to underlying diagnosis, hence risk factors for progression were assessed in stratified analyses and formal interactions by diagnosis were performed. Among non-glomerular patients and after adjusting for baseline GFR, times to the composite event were significantly reduced with Up/c > 2 mg/mg, hypoalbuminemia, elevated blood pressure, dyslipidemia, male gender and anemia by 79%, 69%, 38%, 40%, 38% and 45%, respectively. Among patients with glomerular disease, Up/c > 0.5 mg/mg, hypoalbuminemia and elevated blood pressure significantly reduced times to the composite event by 94%, 71% and 67%, respectively. Variables expressing change in patient clinical status over the initial year of the study contributed significantly to the model which was cross validated internally.

Limitations—small number of events in glomerular patients and use of internal cross validation.

Conclusions—Characterization and modeling of risk factors for CKD progression can be used to predict the extent to which these factors, either alone or in combination, would shorten the time to RRT/50% decline of GFR in children with CKD.

Keywords

pediatric; kidney; progression; glomerular; proteinuria

Introduction

Chronic kidney disease (CKD) is currently estimated to affect 16% of the general U.S. population and is destined to affect nearly 60% of the U.S. population during their lifetime.^{1,2} While children represent only a small proportion of those with CKD, affected children pose unique challenges to the health care system and to their providers, who must address not only the primary renal disorder, but the many extrarenal manifestations of CKD that complicate management.^{3,4} Most importantly, the development of end-stage renal disease (ESRD) compromises the life expectancy of affected patients, with an age-specific mortality rate for children receiving dialysis that is 30 to 150 times higher than for healthy children.^{1,3,5,6}

Scant epidemiologic data exist about the progression of CKD in children. Two prior European studies have demonstrated a relationship between the presence of proteinuria and elevated blood pressure and the progression of CKD in children.^{7,8} Cross-sectional data from the Chronic Kidney Disease in Children (CKiD) study showed that for every 10% decrease in directly measured glomerular filtration rate (GFR), the urine protein/creatinine was higher by an average of 14%, regardless of CKD etiology.⁹ The present reports provides longitudinal data from the CKiD cohort study, identifying predictors of disease progression

in children with mild-to-moderate CKD studied by repeated direct measurement of GFR. These data have also facilitated development of a validated time to composite endpoint model.

Materials and Methods

Study participants and design

The CKiD study design, methods and baseline characteristics of the cohort have been described previously.^{10,11} Patients 1–16 years of age with an estimated GFR of 30 to 90 ml/min per 1.73 m² were enrolled from 54 participating centers. The study entry (V1) visits occurred between January 2005 and July 2009, with the 1-year follow-up visits (V2; baseline for current analysis) occurring between January 2006 and August 2010. For study visit frequency and measurements, inclusion and exclusion criteria, and a list of participating centers, see Tables S1–S3 in the online appendix.

Patient Data

Patient data included family income, birth history (premature, small for gestational age, low birth weight) and primary CKD diagnosis (glomerular or non-glomerular). Height was determined by averaging three stadiometric measures at each study visit for children > 2 years of age. Younger children were measured while lying supine. BP was determined at each visit as the average of three auscultatory measurements obtained with an aneroid sphygmomanometer, as described previously.¹²

GFR Measurement, Biomarker Assays and other Parameters

Body surface area (BSA) scaled GFR was determined from plasma iohexol disappearance curves at study entry, one year later, and every other year thereafter using previously reported methods.^{13,14} When GFR could not be directly measured, it was estimated (eGFR) using published equations derived from the CKiD population.¹⁵ GFR-related biomarkers were determined at the central CKiD laboratory at the University of Rochester. Serum creatinine (enzymatic), BUN and renal function panel (serum sodium, potassium, calcium and phosphorus) were analyzed on a Bayer Advia 2400 analyzer (Siemens Diagnostics, Tarrytown NY) and cystatin C was determined by nephelometry (Siemens Dade-Behring). Serum CO₂ was obtained locally. Serum albumin was determined annually by the bromocresol green binding method. A complete blood count was measured locally, while urine protein and creatinine were measured centrally. Details of the techniques used to measure the first morning urine protein/creatinine (Up/c) have previously been published.⁹ Fasting serum triglycerides (TG) and total cholesterol (TC) were determined at V2 using routine enzymatic methods; HDL-C was analyzed by the Bayer analyzer, as previously described.¹⁶

The CKD diagnoses were reviewed by the members of the CKiD Steering Committee and categorized as either glomerular or non-glomerular etiology. The specific diagnoses are listed in Table S4 (online supplement).

Covariate Definitions

Laboratory values collected at V2 were examined both as continuous and categorical variables using clinically relevant cutpoints. The participant's severity of CKD was classified by strata delineated by the KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease.¹⁷ Anemia was defined as a hemoglobin < 5th percentile using age and sex specific norms.¹⁸ Proteinuria was defined by the Up/c as normal/minimal (Up/c < 0.5mg/mg), elevated (Up/c 0.5–2.0mg/mg) or nephrotic-range (Up/c > 2.0mg/mg). Hypoalbuminemia was defined as serum albumin < 3.8g/dL.¹⁹ Elevated serum phosphate was defined as > 6.5mg/dL for children <13 years old and > 4.5mg/dL for children > 13 years.^{20,21} Elevated serum potassium was defined as > 5.2mEq/L and acidosis was defined as serum CO₂ < 22 mEq/L.¹⁹ Dyslipidemia was defined as TG > 130 mg/dl, HDL-C < 40 mg/dl or non-HDL-C > 160 mg/dl.¹⁶ Elevated blood pressure was defined as systolic or diastolic BP > the 90th percentile for age, gender, and height, based on the National High Blood Pressure Education Program Fourth Report prehypertension and hypertension categories.²² We also examined high normal blood pressure (hBP), defined as systolic or diastolic BP from the 50th to the 90th percentile. Data pertaining to birth history characterization as premature (< 36 weeks gestation), low birth weight (< 2500 g), or SGA (birth weight <10th percentile for gestational age) were also collected.²³

Statistical Analysis

All analyses were anchored at V2 to allow for the evaluation of both baseline levels and rates of change of covariates as predictors of CKD progression. Changes in variable values from V1 to V2 were described using cutpoints to facilitate grouping of individuals into 4 categories: 1) below the threshold at both V1 and V2, 2) above the threshold at V1 but below at V2, 3) below the threshold at V1 but above at V2 and 4) above the threshold at both visits. The exception was GFR, for which change was characterized using the continuous ratio of the V2 GFR to V1 GFR.

Definition and Ascertainment of Outcome

Progression of kidney dysfunction was defined as either initiation of RRT (dialysis or transplant) or a 50% reduction of GFR from the V2 observed level, the two outcomes comprising the composite event. If a 50% reduction of GFR occurred between two study visits, interpolation between the two GFR values surrounding the event was used to determine the time point of halving. Multivariate parametric failure time models assuming a log normal distribution of failure times were used to evaluate the unadjusted and adjusted associations between baseline covariate levels, as well as rates of change of covariates and the composite event. We used a lognormal regression approach as we have previously found a lack of proportionality of the hazards with respect to the exposure of proteinuria for the outcome of end-stage renal disease. Additionally, the parametric approach provides a means to communicate the results in terms of relative times to an event, a clinically relevant concept to communicate to both clinicians and patients with kidney disease.

The data of the i th child were the time t_i from baseline (V2) to either the composite event (coded as $e_i = 1$) or to last time seen event-free (coded as $e_i = 0$) and the constellation of

predictors x_i . Lognormal regression methods were used to evaluate the associations between baseline covariate levels, as well as rates of change of covariates and the time to the composite event (i.e., p% develop event at $\exp(\beta x_i + \sigma Z_p)$ where β and σ are location and scale parameters, and Z_p is the pth percentile of a standard normal variate (e.g., $Z_{0.975} = 1.96$).²⁴ The strength of association was expressed in terms of relative times, which can be interpreted as the relative change in the length of time until the participant would, on average, experience the composite event, comparing exposed to unexposed (e.g. 0.5 relative time would indicate halving of the event time comparing exposed to unexposed). The model can be extended to allow the scale parameter to also depend on predictors.²⁴

Models were validated using cross validation methods, with the data divided into ten random samples of 10% of the data. Excluding each 10% sample in turn, parameters were estimated in the remaining 90% of the data. Then, in the excluded 10% sample, the standardized survival times w_i were calculated as $[\exp^{-\beta x_i t_i}]^{1/\sigma}$. Assuming an accurate prediction, these times should correspond to a sample subjected to censoring from the standard lognormal ($LN[0,1]$) distribution. The correspondence was assessed graphically by comparing the non-parametric Kaplan-Meier curve of the standardized times against the survival function of the standard lognormal $LN[0,1]$. All conventional models were fit using SAS Version 9.2 for Windows (SAS Institute Inc, Cary, NC, USA) while the lognormal models with heterogeneous scales and the validation analysis was performed using TIBCO Spotfire S+ 8.2 for Windows. Figures were created in R 2.15.2.

The study design and conduct was approved by the internal review boards for each of the participating centers and by an external advisory committee appointed by the National Institutes of Health. Written informed consent/assent was obtained from all participants/families according to local requirements.

Results

The study population consisted of 496 participants, 398 with a non-glomerular and 98 with a glomerular etiology of CKD. There were 69 children that were lost to follow-up during the period of observation: 28 were withdrawn from the study by the clinical site, 2 withdrawn due to pregnancy and 39 disenrollments. At baseline (V2), iohexol GFR (iGFR) was obtained for 447/496 participants (90%). eGFR was calculated for the 49 patients for whom an iGFR was not available.

Baseline Characteristics and Covariates

Baseline characteristics and covariates of the participants are described in Table 1, which also illustrates the baseline differences between children with non-glomerular and glomerular disease, respectively. Specifically, patients with non-glomerular disease had significantly greater values for male gender, serum albumin, phosphate, hemoglobin, percentage of subjects with low birth weight and years of follow-up compared to patients with glomerular disease. In contrast, subjects with glomerular disorders had greater values for median age, percentage of patients of African-American race, serum creatinine, urine p/c, and percentage of patients with hypoalbuminemia, anemia and dyslipidemia, compared to those with non-glomerular disease.

Baseline Covariates and Time to Composite Event

The impact of the baseline (V2) GFR level on time to the composite event was determined. In the univariate analyses and compared to those with a $\text{GFR} > 45 \text{ ml/min/1.73 m}^2$, a GFR between 30 and 45 ml/min/1.73 m^2 shortened the time to an event by 70% and 91% ($P < 0.001$) among children with non-glomerular and glomerular disease, respectively. A GFR $< 30 \text{ ml/min/1.73 m}^2$ shortened the time to event by 90% and 97% ($P < 0.001$), respectively for non-glomerular and glomerular patients, compared to those with a $\text{GFR} > 45$. Figure S1 (online supplement) displays both nonparametric (Kaplan Meier) and parametric (lognormal) survival function estimates, and depicts the effect of baseline GFR on both groups.

The impact of a variety of baseline risk factors on time to the composite event is shown in Table 2. In univariate analysis, elevated or nephrotic range proteinuria, elevated phosphate, elevated potassium, elevated BP, anemia, and dyslipidemia were predictors of more rapid progression for children with both non-glomerular and glomerular disease. Acidosis was also predictive in the non-glomerular group. Several risk factors (i.e., male sex, proteinuria, elevated phosphate and elevated blood pressure) showed differential effects according to diagnosis group. Indeed, formal test for interaction between proteinuria and diagnosis group showed a strong level of significance for elevated ($p = 0.014$) and nephrotic-range proteinuria ($p = 0.002$).

In the baseline GFR adjusted models shown in Table 2, all of the predictive factors for the non-glomerular group except for potassium and acidosis remained significant and hypoalbuminemia became significant. In this group of patients, elevated and nephrotic range proteinuria reduced the average time to event by 41% and 79%, respectively, compared to those with a $\text{Up/c} < 0.5$ ($P < 0.001$) confirming the strong association of Up/c with time to ESRD depicted in the left panel of Figure 1. Children with hypoalbuminemia, hyperphosphatemia, elevated BP, anemia, and dyslipidemia had times to the composite event that were 69%, 36%, 38%, 45%, and 40% shorter compared to those without these characteristics. Male gender and older age also predicted a shorter time to event among the non-glomerular patients. For the glomerular group after adjusting for baseline GFR, elevated phosphate, elevated potassium, anemia, and dyslipidemia were no longer significant. In contrast, elevated and nephrotic range proteinuria exerted the greatest influence, shortening the average time to an event by 78% and 94%, respectively compared to those with a $\text{Up/c} < 0.5$ ($P < 0.001$) confirming the strong association of Up/c with time to ESRD depicted in the right panel of Figure 1. In addition, hypoalbuminemia and elevated BP significantly shortened the event-free times by 71% and 67%, respectively.

Time Dependent Covariates and Time to Composite Event

Results of the models which permitted determination of the impact of any change in variables between study visits V1 and V2 on the relative time to the composite event are described in Table 3. The models were adjusted for the significant baseline factors (bolded factors in Table 2, data columns 2 and 4) and GFR level. In these models, persistence of nephrotic range proteinuria, anemia and ACE/ARB use were important predictors of a

shortened time to the composite event for children with a non-glomerular diagnosis. For children with a glomerular diagnosis, persistent anemia was predictive.

Final models were subsequently composed of the significant change variables, with the aforementioned exceptions added to the baseline variable models, to facilitate prediction of time to event; GFR categories were collapsed to a dichotomous representation (GFR<45) among glomerular children based on similar results for the GFR<30 and 30 GFR<45 ml/min/1.73m² categories.

Among children with a non-glomerular diagnosis, the log-transformed times to the composite event of 50% GFR decline/ RRT are normally distributed with mean $M_{NG} = 3.58 - 0.03 (AGE \text{ in years}) - 0.20 (MALE) - 0.27 (GFR \text{ 30 to 45}) - 0.83 (GFR < 30) - 0.67 (Hypoalbuminemia) - 0.32 (BP > 90th \text{ percentile}) - 0.15 (Dyslipidemia) - 0.77 (Nephrotic Proteinuria Resolution) - 1.07 (Proteinuria Onset) - 1.19 (Persistent Nephrotic Proteinuria) - 0.30 (Anemia Resolution) - 0.40 (Anemia Onset) - 0.56 (Persistent Anemia) - 0.05 (ACEARB Discontinuation) - 0.51 (ACEARB Initiation) - 0.31 (Persistent ACEARB use)$; and standard deviation of 0.81, 0.98 and 1.21 for GFR > 45, GFR between 30 and 45 and GFR < 30 ml/min/1.73 m² respectively. The median time when the composite event is expected to occur is the antilog of M_{NG} . The antilog of the coefficients of the variables quantify the reduction of time to composite event due to the particular predictor (e.g., males had $0.82 = \exp(-0.20)$ the length of time that females take to composite event).

Similarly, among children with a glomerular diagnosis, the log-transformed times to the composite event of 50% GFR decline/ RRT are normally distributed with mean $M_G = 3.97 - 2.01 (GFR < 45) - 0.38 (Hypoalbuminemia) - 0.60 (BP > 90th \text{ percentile}) - 2.37 (Nephrotic Proteinuria Resolution) - 1.17 (Nephrotic Proteinuria Onset) - 1.35 (Persistent Nephrotic Proteinuria) - 0.18 (Anemia Resolution) - 0.37 (Anemia Onset) - 1.16 (Persistent Anemia)$; and standard deviation 1.62. The median time when the composite event is expected to occur is the antilog of M_G . The antilog of the coefficients of the variables quantify the reduction of time to composite event due to the particular predictor (e.g., those with GFR<45 had $0.13 = \exp(-2.01)$ the length of time that those with GFR>45 take to composite event).

Most importantly, these models were validated in a test set of data created using cross validation methods and showed excellent agreement (i.e. the 95% confidence interval of the standardized survival times encompass the expected lognormal survival function) between the predicted standardized times from the model and the expected standardized times in the cross-validation dataset as seen in Figure 2. Given the satisfactory validation results, we can use the final models to predict survival times for children in our study given their clinical profiles, as reflected by the data displayed in Figure 3.

Likewise, we can apply these formulae to look at the potential lengthening of time to either RRT or GFR halving that would result from treating a modifiable clinical risk factor, for example treating nephrotic range proteinuria and reducing the urine protein to creatinine ratio below 2.0. Given an average child in our study with a non-glomerular diagnosis at the median of the distribution of times to the event, resolving nephrotic range proteinuria would

potentially result in an additional 2 years of time prior to RRT or GFR halving compared to the same child with persistent nephrotic range proteinuria. This corresponds to a 1.5 times increase in the time to RRT or GFR halving.

Discussion

The present work delineates a number of factors that increase the risk for and shorten the time to a composite event in children with CKD. It has been known that the time course for the development and progression of CKD can be variable and is likely impacted by a number of potentially modifiable and unmodifiable risk factors which, to date, have been infrequently investigated in children.^{7,8,25–27} Clear delineation of the specific modifiable factors that impact CKD progression, as accomplished here, is crucial if successful therapeutic interventions to prevent or delay the course of CKD are to be developed and implemented early in the course of the disorder.²⁸

Our analysis, based upon repeated direct measurement of GFR, revealed that nephrotic range proteinuria and lower values for GFR at baseline were predictors of progression to the composite event for patients with either glomerular or non-glomerular disease. Proteinuria has also been an independent predictor of progressive CKD in several other pediatric studies.^{7,8,29} In the ItalKid Project, higher baseline Up/c correlated with a faster decline in estimated GFR in patients with congenital hypodysplasia, as we saw with our cohort.⁸ The lack of correlation between the baseline GFR and progression in the Italian study contrasts with our results and is likely due to their use of an imprecise estimation of kidney function vs. our precise measurement of GFR by iothexol disappearance. Whereas the ESCAPE trial and the recent retrospective study of Cerqueira, et al. also used an estimated GFR, they too found that a low baseline value and a greater degree of proteinuria were associated with an increased overall risk for CKD progression.^{7,30}

The relationship that we demonstrated between baseline BP level and the composite event is consistent with the results of the ESCAPE trial, which provided evidence that intensified blood pressure control slows CKD progression in children.⁷ Our finding that elevated BP was associated with accelerated GFR decline in this cohort of children with CKD emphasizes the importance of improved BP control in ameliorating progression. Noteworthy is the finding that the effect of elevated BP was greater in glomerular patients than in the non-glomerular patients, further emphasizing the importance of aggressive BP management, particularly in patients with glomerular causes of CKD.

Dyslipidemia at baseline was also predictive of the composite event in both patient groups. Prior studies have demonstrated a relationship between lipids and CKD and suggest that the degree of dyslipidemia correlates with the degree of renal functional deterioration.^{16,31} Likewise, the presence of acidosis in the non-glomerular patients, as commonly occurs in this group of disorders and which has been associated with CKD progression in adults, was also predictive of progression in our cohort.²⁷ The independent relationship between elevated phosphorus levels and CKD progression in children has previously been demonstrated by the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), as well as in adult studies by Voormolen et al., and Di Iorio et al. The latter

study suggested that hyperphosphatemia may inhibit the beneficial glomerular hemodynamic response to therapeutic ACE inhibition.^{32–34}

Evaluation of our patients' biomarkers over time revealed the significant role that persistence of a variety of clinical abnormalities has on CKD progression. Anemia was one such factor, and appears to be a surrogate marker for tissue hypoxia that might perpetuate preexisting renal tissue damage by stimulating extra-cellular matrix production and the release of profibrotic cytokines.^{35,36}

Our use of lognormal regression methods was uniquely informative as this novel approach, which was internally validated using the CKiD cohort and cross validation methods, made it possible for us to predict the extent to which a variety of factors, either alone or in combination, would shorten the time to the composite event. This is in contrast to standard hazard ratios, which provide means for comparison but have limited use for summarization and prediction. In addition, we have previously shown the lack of proportionality of the hazards for the effect of proteinuria (a key predictor of the composite event) on the event of end-stage renal disease.³⁷ The clinical importance of assessing the combined impact of multiple factors has also recently been emphasized in community-based studies of CKD in adults.^{38,39} Compared to prior studies in children, our ability to delineate the graded impact of proteinuria on progression was also noteworthy, as both elevated and nephrotic range proteinuria contributed to a significantly more rapid progression to the composite event.⁴⁰ Finally, to our knowledge, this is the first use of a time-to-event analysis in cohort studies of pediatric CKD supported by directly measured GFR. The availability of these time-to-event data has significant clinical implications as they can facilitate the timely introduction of patient/family education based on an individualized clinical risk profile of progressive CKD, as well as ultimately providing a means by which the impact of a therapeutic intervention can be measured.^{41–43}

A limitation of our study is that the predictions of time to composite event apply specifically to the CKiD cohort as we used an internal cross validation approach. However, the clinical spectrum of disease displayed by this cohort is felt to be representative of the pediatric CKD population at large. Whereas a strength of our study has been our capacity to prospectively follow a large pediatric patient cohort with mild-moderate CKD at study entry, the subgroup with glomerular disease was relatively small and with only 40 events observed, it is possible that our multivariate models are over-fit to the data such that inferences may not generalize to other populations. Most importantly, however, for the first time ever in a study of pediatric CKD, we conducted repeated direct measurements of GFR to characterize and compare patients who did and did not progress to a composite event. The availability of measured GFR values from > 90% of our patients is unique for a study of CKD progression in children and substantially contributes to the accuracy of our findings.¹³ Even when excluding the 49 children for whom we used estimated GFR, the results for the multivariate lognormal models are similar. Finally, the ability to follow children with both glomerular and non-glomerular disorders has also been important because of the differences in the natural history of the two patient groups, as has previously been documented.⁴⁴

In conclusion, this large, prospective cohort study provides evidence that in pediatric patients with CKD there are a number of well-defined and potentially modifiable factors that significantly and predictably shorten the time to RRT/50% decline in GFR. Continued evaluation of this cohort should make it possible to further refine our understanding of the identity and impact of risk factors for progression, and inform the design of intervention trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Data in this manuscript were collected by the Chronic Kidney Disease in children prospective cohort study (CKiD) with clinical coordinating centers (Principal Investigators) at Children's Mercy Hospital and the University of Missouri – Kansas City (Bradley A. Warady, MD) and Children's Hospital of Philadelphia (Susan Furth, MD, Ph.D.), Central Biochemistry Laboratory at the University of Rochester Medical Center (George J. Schwartz, MD), and data coordinating center at the Johns Hopkins Bloomberg School of Public Health (Alvaro Muñoz, Ph.D.). The CKiD Study is supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, with additional funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U01-DK-66143, U01-DK-66174, U01DK-082194, U01-DK-66116). The CKiD website is located at <http://www.statepi.jhsph.edu/ckid>.

The authors would also like to acknowledge the substantial contributions of all of the investigators and coordinators in CKiD, in addition to all of the participating patients and their families.

REFERENCES

1. U.S. Renal Data System. National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD: 2013. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health.
2. Grams ME, Chow EK, Segev DL, Coresh J. Lifetime incidence of CKD stages 3–5 in the United States. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2013; 62:245–252. [PubMed: 23566637]
3. Warady BA, Chadha V. Chronic kidney disease in children: the global perspective. *Pediatric nephrology (Berlin, Germany)*. 2007; 22:1999–2009.
4. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. *Pediatric nephrology (Berlin, Germany)*. 2012; 27:363–373.
5. McDonald SP, Craig JC. Long-term survival of children with end-stage renal disease. *The New England journal of medicine*. 2004; 350:2654–2662. [PubMed: 15215481]
6. Mitsnefes MM, Laskin BL, Dahhou M, Zhang X, Foster BJ. Mortality risk among children initially treated with dialysis for end-stage kidney disease, 1990–2010. *JAMA : the journal of the American Medical Association*. 2013; 309:1921–1929. [PubMed: 23645144]
7. Wuhl E, Trivelli A, Picca S, et al. Strict blood-pressure control and progression of renal failure in children. *The New England journal of medicine*. 2009; 361:1639–1650. [PubMed: 19846849]
8. Ardissino G, Testa S, Dacco V, et al. Proteinuria as a predictor of disease progression in children with hypodysplastic nephropathy Data from the Ital Kid Project. *Pediatric nephrology (Berlin, Germany)*. 2004; 19:172–177.
9. Wong CS, Pierce CB, Cole SR, et al. Association of proteinuria with race, cause of chronic kidney disease, and glomerular filtration rate in the chronic kidney disease in children study. *Clinical journal of the American Society of Nephrology : CJASN*. 2009; 4:812–819. [PubMed: 19297612]
10. Furth SL, Cole SR, Moxey-Mims M, et al. Design and methods of the Chronic Kidney Disease in Children (CKiD) prospective cohort study. *Clinical journal of the American Society of Nephrology : CJASN*. 2006; 1:1006–1015. [PubMed: 17699320]

11. Furth SL, Abraham AG, Jerry-Fluker J, et al. Metabolic abnormalities, cardiovascular disease risk factors, and GFR decline in children with chronic kidney disease. *Clinical journal of the American Society of Nephrology : CJASN*. 2011; 6:2132–2140. [PubMed: 21841064]
12. Flynn JT, Mitsnefes M, Pierce C, et al. Blood pressure in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children study. *Hypertension*. 2008; 52:631–637. [PubMed: 18725579]
13. Schwartz GJ, Abraham AG, Furth SL, Warady BA, Munoz A. Optimizing iohexol plasma disappearance curves to measure the glomerular filtration rate in children with chronic kidney disease. *Kidney international*. 2010; 77:65–71. [PubMed: 19847157]
14. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *The Journal of pediatrics*. 1978; 93:62–66. [PubMed: 650346]
15. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *Journal of the American Society of Nephrology : JASN*. 2009; 20:629–637. [PubMed: 19158356]
16. Saland JM, Pierce CB, Mitsnefes MM, et al. Dyslipidemia in children with chronic kidney disease. *Kidney international*. 2010; 78:1154–1163. [PubMed: 20736985]
17. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease. *Kidney international Supplement*. 2013; 3:1–150.
18. Hollowell JG, van Assendelft OW, Gunter EW, Lewis BG, Najjar M, Pfeiffer C. Hematological and iron-related analytes--reference data for persons aged 1 year and over: United States, 1988–94. *Vital and health statistics Series 11, Data from the national health survey*. 2005:1–156.
19. KDOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2000; 35:S1–S140. [PubMed: 10895784]
20. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2009; 53:S1.
21. KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children with Chronic Kidney Disease. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2005; 46:S1–S122.
22. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2004; 114:555–576. [PubMed: 15286277]
23. Greenbaum LA, Munoz A, Schneider MF, et al. The association between abnormal birth history and growth in children with CKD. *Clinical journal of the American Society of Nephrology : CJASN*. 2011; 6:14–21. [PubMed: 21030583]
24. Cox C, Chu H, Schneider MF, Munoz A. Parametric survival analysis and taxonomy of hazard functions for the generalized gamma distribution. *Statistics in medicine*. 2007; 26:4352–4374. [PubMed: 17342754]
25. Quirino IG, Dias CS, Vasconcelos MA, et al. A predictive model of chronic kidney disease in patients with congenital anomalies of the kidney and urinary tract. *Pediatric nephrology (Berlin, Germany)*. 2014; 29:2357–2364.
26. Kummer S, von Gersdorff G, Kemper MJ, Oh J. The influence of gender and sexual hormones on incidence and outcome of chronic kidney disease. *Pediatric nephrology (Berlin, Germany)*. 2012; 27:1213–1219.
27. Dobre M, Yang W, Chen J, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the Chronic Renal Insufficiency Cohort (CRIC) study. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2013; 62:670–678. [PubMed: 23489677]
28. Noone D, Licht C. Chronic kidney disease: a new look at pathogenetic mechanisms and treatment options. *Pediatric nephrology (Berlin, Germany)*. 2013
29. Wingen AM, Fabian-Bach C, Schaefer F, Mehls O. Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children European Study Group of Nutritional

- Treatment of Chronic Renal Failure in Childhood. *Lancet*. 1997; 349:1117–1123. [PubMed: 9113009]
30. Cerqueira DC, Soares CM, Silva VR, et al. A Predictive Model of Progression of CKD to ESRD in a Predialysis Pediatric Interdisciplinary Program. *Clinical journal of the American Society of Nephrology : CJASN*. 2014
 31. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. *Kidney international*. 2000; 58:293–301. [PubMed: 10886574]
 32. Staples AO, Greenbaum LA, Smith JM, et al. Association between clinical risk factors and progression of chronic kidney disease in children. *Clinical journal of the American Society of Nephrology : CJASN*. 2010; 5:2172–2179. [PubMed: 20813855]
 33. Di Iorio BR, Bellizzi V, Bellasi A, et al. Phosphate attenuates the anti-proteinuric effect of very low-protein diet in CKD patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2013; 28:632–640.
 34. Voormolen N, Noordzij M, Grootendorst DC, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2007; 22:2909–2916.
 35. Furth SL, Cole SR, Fadrowski JJ, et al. The association of anemia and hypoalbuminemia with accelerated decline in GFR among adolescents with chronic kidney disease. *Pediatric nephrology (Berlin, Germany)*. 2007; 22:265–271.
 36. Rossert J, Levin A, Roger SD, et al. Effect of early correction of anemia on the progression of CKD. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2006; 47:738–750. [PubMed: 16632012]
 37. Munoz, A.; Abraham, A.; Matheson, M.; Wada, N. Non-proportionality of hazards in the competing risks framework. In: Lee, MI.; Gail, M.; Pfeiffer, R.; Satten, G.; Cai, T.; Gandy, A., editors. *Risk Assessment and Evaluation of Predictions*. First Edition. New York: Springer Science+Business Media, LLC; 2013.
 38. Turin TC, James M, Ravani P, et al. Proteinuria and rate of change in kidney function in a community-based population. *Journal of the American Society of Nephrology : JASN*. 2013; 24:1661–1667. [PubMed: 23833255]
 39. Cozzolino M, Gentile G, Mazzaferro S, Brancaccio D, Ruggenenti P, Remuzzi G. Blood pressure, proteinuria, and phosphate as risk factors for progressive kidney disease: a hypothesis. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2013; 62:984–992. [PubMed: 23664548]
 40. de Goeij MC, Liem M, de Jager DJ, et al. Proteinuria as a risk marker for the progression of chronic kidney disease in patients on predialysis care and the role of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker treatment. *Nephron Clinical practice*. 2012; 121:c73–c82. [PubMed: 23128440]
 41. Webb NJ, Shahinfar S, Wells TG, et al. Losartan and enalapril are comparable in reducing proteinuria in children. *Kidney international*. 2012; 82:819–826. [PubMed: 22739977]
 42. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2013; 185:949–957.
 43. De Nicola L, Conte G, Russo D, Gorini A, Minutolo R. Antiproteinuric effect of add-on paricalcitol in CKD patients under maximal tolerated inhibition of renin-angiotensin system: a prospective observational study. *BMC nephrology*. 2012; 13:150. [PubMed: 23167771]
 44. Ardissino G, Vigano S, Testa S, et al. No clear evidence of ACEi efficacy on the progression of chronic kidney disease in children with hypodysplastic nephropathy--report from the Italkid Project database. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2007; 22:2525–2530.

Figure 1.

Kaplan-Meier and lognormal survival curves for composite event (50% GFR decline or renal replacement therapy) of baseline urine protein/creatinine for glomerular and non-glomerular subjects.

Figure 2. Kaplan Meier curves showing the predicted standardized times of the composite event resulting from the cross-validation. The expected lognormal survival curve, which is overlaid on top of the predicted survival function, is entirely encompassed inside the 95% confidence intervals of the prediction for both glomerular and non-glomerular children.

Figure 3.

Estimates of survival curves for composite event (50% GFR decline or renal replacement therapy) based on lognormal models of children with different constellations of clinical variables for glomerular and non-glomerular subjects. **Values of variables in the models not listed in the figure are considered not present (i.e., zero).**

Table 1

Descriptive statistics (median [interquartile range] or % (N)) of the participants from the CKiD cohort using data from the second annual (baseline) visit

Baseline Characteristic: Demographics and Clinical Characteristics	CKD Diagnosis	
	Non-Glomerular CKD (N=398)	Glomerular CKD (N=98)
Age, years	11 [8, 15] [§]	15 [12, 17] [§]
Male sex, %	64% (256) [§]	48% (47) [§]
African American race, %	19% (76) [§]	36% (35) [§]
Household Income		
\$36,000/yr	40% (155)	41% (39)
36–75,000/yr	31% (123)	33% (31)
>\$75,000/yr	29% (113)	26% (24)
Height z-score	−0.7 [−1.4, −0.0]	−0.6 [−1.2, 0.3]
<2 SDs	12% (44)	10% (10)
GFR, ml/min/1.73 m ²	45 [33, 58]	48 [33, 64]
Stage 1 to 2 (> 60)	21% (82)	29% (28)
Stage 3a (45 to 60)	28% (109)	25% (24)
Stage 3b (30 to 45)	33% (131)	29% (28)
Stage 4 to 5 (<= 30)	18% (73)	18% (17)
Serum Creatinine, mg/dL	1.3 [0.9, 1.8] [§]	1.4 [1.1, 2.0] [§]
Cystatin C, mg/L	1.6 [1.3, 2.3]	1.5 [1.2, 2.2]
Up/c	0.35 [0.15, 0.90] [§]	0.86 [0.25, 1.80] [§]
Minimal (<0.5)	60% (225) [§]	39% (36) [§]
Elevated (0.5 to 2)	31% (118) [§]	42% (39) [§]
Nephrotic (> 2)	9% (35) [§]	18% (17) [§]
tCO ₂ , mmol/L	21 [19, 23]	21 [19, 23]
Acidotic (< 22)	56% (222)	56% (54)
Albumin, g/dL	4.4 [4.2, 4.6] [§]	4.1 [3.9, 4.4] [§]
Hypoalbuminuria (<3.8)	2% (9) [§]	21% (20) [§]
Phosphate, mg/L	4.8 [4.2, 5.1] [§]	4.3 [3.8, 5.1] [§]
Elevated (see methods)	18% (69)	23% (22)
Potassium, mg/L	4.4 [4.2, 4.8]	4.5 [4.2, 5.0]
Elevated (> 5.2)	9% (34)	12% (11)
SBP Percentile	62 [35, 84]	61 [26, 84]
DBP Percentile	65 [41, 87]	58 [31, 88]
Overall BP category, %ile		
Normal (<50 th)	27% (109)	29% (28)

	CKD Diagnosis	
Baseline Characteristic: Demographics and Clinical Characteristics	Non-Glomerular CKD (N=398)	Glomerular CKD (N=98)
High-normal (50 th to 90 th)	47% (187)	45% (44)
Elevated (> 90 th)	26% (102)	27% (26)
Hemoglobin , %ile	12.8 [12.0, 13.8] [§]	12.4 [11.5, 13.1] [§]
Anemia (< 5 th)	26% (102) [§]	43% (39) [§]
Dyslipidemia (see methods)	42% (160) [§]	56% (54) [§]
Low Birth Weight (<2500 gms)	21% (80) [§]	11% (10) [§]
Premature (< 36 weeks)	14% (54)	9% (9)
Small for Gestational Age (< 10 th %ile)	20% (74)	17% (15)
Years of follow-up	5.2 [3.7, 6.2] [§]	3.7 [1.6, 5.4] [§]

[§]Non-Glomerular and Glomerular group values significantly different at the $\alpha=0.05$ level from a Wilcoxon two-sample test (continuous variables) or χ^2 test (categorical variables). Hypoalbuminemia, elevated potassium, low birth weight and prematurity were tested using an Exact test due to small number of events.

Table 2

Effect of Baseline Risk Factor Levels on Time to Event

	Relative Times (95% CI) to RRT/death or 50% decline in GFR			
	Non-Glomerular		Glomerular	
	Unadjusted	V2 GFR level adjusted ^I	Unadjusted	V2 GFR level adjusted ^I
Age, years	0.91 (0.87, 0.95)	0.95 (0.90, 0.99)	0.95 (0.81, 1.11)	0.91 (0.80, 1.04)
Male sex	0.57 (0.37, 0.88)	0.62 (0.42, 0.92)	0.85 (0.27, 2.63)	1.15 (0.45, 2.97)
AA race	0.79 (0.47, 1.31)	0.66 (0.42, 1.03)	0.87 (0.27, 2.84)	0.44 (0.17, 1.16)
Household Income (\$36,000, ref)				
36–75,000/yr	1.28 (0.76, 2.17)	1.32 (0.82, 2.11)	0.50 (0.10, 2.41)	1.31 (0.37, 4.62)
\$36,000/yr	1.04 (0.63, 1.71)	1.02 (0.65, 1.58)	0.43 (0.09, 1.94)	0.72 (0.22, 2.37)
Height z-score				
<2 SDs	0.80 (0.46, 1.41)	0.96 (0.58, 1.59)	0.19 (0.04, 1.01)	0.38 (0.10, 1.50)
Low Birth Weight	1.04 (0.62, 1.73)	0.92 (0.58, 1.46)	0.29 (0.05, 1.66)	0.66 (0.16, 2.66)
Premature	0.69 (0.39, 1.21)	0.80 (0.48, 1.34)	1.07 (0.14, 8.09)	0.42 (0.08, 2.12)
Small for Gestational Age	1.26 (0.74, 2.15)	1.20 (0.75, 1.93)	0.68 (0.15, 3.14)	1.04 (0.30, 3.59)
Blood Pressure (normal, ref)				
High-normal	1.20 (0.80, 1.82)	0.91 (0.63, 1.33)	0.92 (0.31, 2.73)	0.69 (0.27, 1.78)
Elevated	0.62 (0.39, 0.96)	0.62 (0.42, 0.92)	0.15 (0.05, 0.48)	0.33 (0.12, 0.92)
Up/c (<0.5, ref)				
Elevated	0.46 (0.32, 0.67)	0.59 (0.42, 0.82)	0.14 (0.04, 0.49)	0.22 (0.07, 0.69)
Nephrotic	0.12 (0.07, 0.20)	0.21 (0.13, 0.33)	0.01 (0.00, 0.06)	0.06 (0.01, 0.25)
tCO ₂				
Acidotic	0.64 (0.43, 0.96)	0.97 (0.68, 1.38)	0.35 (0.11, 1.11)	0.63 (0.25, 1.61)
Albumin				
Hypoalbuminemia	0.37 (0.12, 1.10)	0.31 (0.12, 0.80)	0.09 (0.03, 0.28)	0.29 (0.10, 0.79)
Phosphate				
Elevated	0.39 (0.25, 0.60)	0.64 (0.42, 0.96)	0.14 (0.04, 0.45)	0.49 (0.17, 1.38)
Potassium				
Elevated	0.30 (0.17, 0.55)	0.60 (0.36, 1.00)	0.17 (0.03, 0.81)	0.82 (0.22, 3.06)
Hemoglobin				
Anemia	0.31 (0.21, 0.46)	0.55 (0.38, 0.80)	0.16 (0.05, 0.49)	0.39 (0.15, 1.02)
Dyslipidemia	0.42 (0.29, 0.62)	0.60 (0.43, 0.85)	0.25 (0.08, 0.79)	0.63 (0.24, 1.67)

Bold indicates 95% confidence interval doesn't contain 1.0.^I Adjusted for V2 ieGFR categories Stage 3b (30 to 45 ml/min) and Stage 4 to 5 (≤ 30 ml/min) with reference group ieGFR > 45 ml/min

Table 3

Relative Times (95% CI) to RRT/death or 50% Decline in GFR Associated with the Effect of Change of Risk Factor Levels

	Non-Glomerular (N=398)		Glomerular CKD (N=98)	
	N (#Events)	Level- adjusted ¹	N (#Events)	Level- adjusted ²
Height z-score <2 SDs				
no/no	316 (89)	1	83 (34)	1
yes/no	7 (2)	1.10 (0.38, 3.22)	2 (0)	--
no/yes	4 (2)	0.73 (0.22, 2.43)	0 (0)	--
yes/yes	40 (14)	0.98 (0.61, 1.58)	10 (5)	0.45 (0.12, 1.68)
Elevated Blood Pressure				
no/no	194 (47)	1	53 (18)	1
yes/no	61 (19)	0.69 (0.45, 1.05)	13 (4)	0.98 (0.27, 3.58)
no/yes	40 (15)	0.66 (0.40, 1.09)	10 (6)	0.27 (0.07, 1.01)
yes/yes	59 (23)	0.66 (0.43, 1.01)	16 (10)	0.91 (0.31, 2.65)
ieGFR ratio (v2/v1a), per 10% decline		0.75 (0.55, 1.07)		0.53 (0.21, 1.33)
Nephrotic Proteinuria				
no/no	317 (73)	1	68 (16)	1
yes/no	13 (6)	0.54 (0.27, 1.07)	6 (4)	0.15 (0.03, 0.78)
no/yes	16 (13)	0.34 (0.19, 0.61)	4 (4)	0.27 (0.03, 2.05)
yes/yes	16 (13)	0.30 (0.16, 0.57)	13 (13)	0.25 (0.05, 1.15)
Acidotic				
no/no	98 (14)	1	25 (9)	1
yes/no	74 (21)	0.67 (0.41, 1.42)	17 (5)	8.10 (1.70, 38.60)
no/yes	71 (18)	0.89 (0.52, 1.51)	20 (11)	1.50 (0.44, 5.15)
yes/yes	151 (60)	0.74 (0.47, 1.16)	34 (15)	1.35 (0.46, 3.95)
Hypoalbuminemia				
no/no	369 (102)	1	70 (22)	1
yes/no	6 (4)	1.00 (0.36, 2.76)	4 (3)	0.37 (0.04, 3.42)
no/yes	9 (5)	0.59 (0.26, 1.37)	7 (5)	0.97 (0.18, 5.28)
yes/yes	0 (0)	--	12 (9)	0.44 (0.11, 1.81)
Elevated Phosphate				
no/no	290 (71)	1	58 (22)	1
yes/no	16 (7)	0.90 (0.45, 1.82)	13 (3)	0.84 (0.20, 3.44)
no/yes	31 (13)	0.73 (0.42, 1.28)	8 (4)	0.50 (0.12, 2.15)
yes/yes	37 (18)	0.65 (0.39, 1.07)	14 (10)	0.67 (0.18, 2.45)
Elevated Potassium				
no/no	315 (74)	1	73 (27)	1
yes/no	25 (11)	0.66 (0.39, 1.13)	9 (4)	1.83 (0.41, 8.16)
no/yes	25 (18)	0.61 (0.37, 1.01)	7 (4)	1.06 (0.22, 5.23)
yes/yes	8 (6)	0.67 (0.30, 1.48)	4 (4)	0.78 (0.11, 5.47)

	Non-Glomerular (N=398)		Glomerular CKD (N=98)	
	N (#Events)	Level- adjusted ¹	N (#Events)	Level- adjusted ²
Anemia				
no/no	235 (42)	1	42 (11)	1
yes/no	42 (16)	0.65 (0.40, 1.06)	42 (3)	0.60 (0.09, 3.97)
no/yes	48 (21)	0.59 (0.38, 0.92)	48 (6)	0.58 (0.15, 2.17)
yes/yes	52 (28)	0.59 (0.38, 0.92)	26 (17)	0.25 (0.08, 0.74)
ACE/ARB use				
no/no	186 (39)	1	14 (8)	1
yes/no	20 (10)	0.77 (0.40, 1.49)	8 (7)	0.39 (0.07, 2.15)
no/yes	36 (14)	0.57 (0.34, 0.95)	0 (0)	—
yes/yes	152 (50)	0.68 (0.48, 0.97)	74 (25)	1.07 (0.26, 4.36)

Bold indicates 95% confidence interval doesn't contain 1.0.

¹ Adjusted for V2 level variables: age, male sex, ieGFR categories Stage 3b (30 to 45 ml/min) and Stage 4 to 5 (≤ 30 ml/min) , Elevated (0.5<Up/c<2.0) and Nephrotic range (Up/c>2.0) proteinuria, hypoalbuminemia, elevated phosphate, hypertension, anemia, and dyslipidemia

² Adjusted for V2 level variables: ieGFR categories Stage 3b (30 to 45 ml/min) and Stage 4 to 5 (≤ 30 ml/min) , Elevated (0.5<Up/c<2.0) and Nephrotic (Up/c>2.0) range proteinuria, hypoalbuminemia, and hypertension