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Original Investigation

Estimating Time to ESRD Using Kidney Failure Risk Equations: Results From the African American Study of Kidney Disease and Hypertension (AASK)

Morgan E. Grams, MD, PhD,[1,2,3] Liang Li, PhD,[4] Tom H. Greene, PhD,[5] Adrienne Tin, PhD,[2] Yingying Sang, MS,[2] W.H. Linda Kao, PhD,[2,3,†] Michael S. Lipkowitz, MD,[6] Jackson T. Wright, MD, PhD,[7] Alex R. Chang, MD, MS,[8] Brad C. Astor, PhD,[9,10] and Lawrence J. Appel, MD[2,4,11]

Background: Planning for renal replacement therapy, such as referral for arteriovenous fistula placement and transplantation, often is guided by level of estimated glomerular filtration rate (eGFR). The use of risk equations might enable more accurate estimation of time to end-stage renal disease (ESRD), thus improving patient care.

Study Design: Prospective observational study.

Setting & Participants: 1,094 participants in the African American Study of Kidney Disease and Hypertension (AASK) cohort.

Predictor: Age, sex, urine protein-creatinine ratio ≥ 1 g/g, *APOL1* high-risk status, and 3-year antecedent eGFR decline.

Outcome: Cumulative incidence of ESRD from 5 different starting points: eGFR of 30 and 15 mL/min/1.73 m^2 and 1-year ESRD risk of 5%, 10%, and 20%, estimated by a published 4-variable kidney failure risk equation.

Results: 566 participants developed eGFR of 30 mL/min/1.73 m^2, 244 developed eGFR of 15 mL/min/1.73 m^2, and 437, 336, and 259 developed 1-year ESRD risks of 5%, 10%, and 20%, respectively. The 1-year cumulative incidence of ESRD was 4.3% from eGFR of 30 mL/min/1.73 m^2, 49.0% from eGFR of 15 mL/min/1.73 m^2, 6.7% from 5% ESRD risk, 15.0% from 10% ESRD risk, and 29% from 20% ESRD risk. From eGFR of 30 mL/min/1.73 m^2, there were several risk factors that predicted ESRD risk. From eGFR of 15 mL/min/1.73 m^2, only level of proteinuria did; median time to ESRD was 9 and 19 months in those with higher and lower proteinuria, respectively. Median times were less variable from corresponding ESRD risk thresholds. For example, median times to ESRD from 20% ESRD risk were 22 and 25 months among those with higher and lower proteinuria, respectively.

Limitations: Relatively homogeneous population of African Americans with hypertensive kidney disease.

Conclusions: Results of the present study suggest the potential benefit of incorporating kidney failure risk equations into clinical care, with selection of a specific threshold guided by its intended use.

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INDEX WORDS: End-stage renal disease (ESRD); estimated glomerular filtration rate (eGFR); proteinuria; kidney failure risk equations; risk; disease trajectory; disease progression; prognosis; clinical decision making; African American Study of Kidney Disease and Hypertension (AASK); hypertensive kidney disease.

Advanced chronic kidney disease (CKD) is associated with mortality and significant morbidity, including decline in kidney function and progression to end-stage renal disease (ESRD).[1-7] Estimating time to ESRD is important for both patient counseling and the timing of interventions. Procedures such as arteriovenous fistula placement and kidney transplantation are considered optimal when implemented before the initiation of dialysis therapy, but there may be unnecessary expense and/or risk in performing these procedures too early in the course of kidney function decline.[8-11] However, the time until ESRD

From the [1]Division of Nephrology, Johns Hopkins University School of Medicine; [2]Department of Epidemiology, Johns Hopkins University School of Public Health; [3]Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, MD; [4]University of Texas MD Anderson Cancer Center, Houston, TX; [5]Division of Clinical Epidemiology, University of Utah School of Medicine, Salt Lake City, UT; [6]Division of Nephrology, Georgetown University School of Medicine, Washington, DC; [7]Department of Medicine, Case Western Reserve University, Cleveland, OH; [8]Division of Nephrology, Geisinger Health System, Danville, PA; Departments of [9]Medicine and [10]Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI; and [11]Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.

[†]Deceased June 15, 2014.

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Address correspondence to Morgan E. Grams, MD, PhD, 2024 E Monument, Rm 2-638, Baltimore, MD 21287. E-mail: mgrams2@jhmi.edu

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often is difficult to estimate because it varies by population and potentially by age, sex, and the presence of certain comorbid conditions.[12-22]

Historically, clinical decision making in nephrology has hinged on level of estimated glomerular filtration rate (eGFR). Guidelines recommend nephrology referral when a patient reaches an eGFR of 30 mL/min/1.73 m^2; transplantation programs typically initiate wait-listing for kidney transplantation when eGFR declines to 20 mL/min/1.73 m^2.[11] Some kidney disease experts have begun to advocate for clinical decision making based on risk probabilities, methods long used in specialties such as cardiology. Kidney failure risk equations have been developed and externally validated,[7,23,24] and the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) guidelines incorporate these equations, recommending the initiation of renal replacement therapy planning in persons with a 1-year risk of ESRD > 10%.[11]

To investigate whether kidney failure risk equations might be useful in informing the timing of interventions in advanced kidney disease, we determined the cumulative incidence of and time to ESRD among participants in the AASK (African American Study of Kidney Disease and Hypertension) cohort from 5 different starting points: 2 eGFR levels (30 and 15 mL/min/1.73 m^2) and three 1-year ESRD risk thresholds (5%, 10%, and 20%) estimated from a kidney failure risk equation. We hypothesized that incidence of and time to ESRD would be less variable between subgroups of age, sex, degree of proteinuria, prior eGFR slope, and *APOL1* risk status when estimated from an incident kidney failure risk threshold compared to the more traditional approach based on eGFR.

METHODS

Study Population

The AASK was designed as a multicenter randomized clinical trial to test the efficacy of 3 antihypertensive medications and 2 levels of blood pressure control.[25] Study participants were African American individuals aged 18 to 70 years with GFRs of 20 to 65 mL/min/1.73 m^2 as measured by renal clearance of I^{125} iothalamate. Persons with diabetes, urine protein-creatinine ratio (PCR) > 2.5 g/g, heart failure, severe systemic disease, or malignant or secondary hypertension were excluded. At the completion of the trial, all individuals who were alive and had not yet initiated renal replacement therapy were invited to continue in the AASK observational cohort study.[26] Of 1,094 original participants, 787 were eligible for the observational cohort study, and 691 agreed. Follow-up range was 3.0 to 6.4 years during the trial phase and 8.8 to 12.4 years during the full study.

For the purposes of the present study, study populations were created for each of 5 starting points: eGFR of 30 mL/min/1.73 m^2, eGFR of 15 mL/min/1.73 m^2, and 1-year ESRD risk of 5%, 10%, and 20%. A participant was included in a given study population at the first study visit (including study visit 1) in which eGFR or 1-year ESRD risk crossed the specified threshold value. By definition, the study populations are not mutually exclusive, and a given participant could be included in all 5 study populations at different times during follow-up. The 1-year risk of ESRD was calculated at each study visit using the 4-variable equation published by Tangri et al,[24] that is, model 3, where 1-year risk $= 1 - (0.987104504)^{e^{[(-0.55668 \times \text{eGFR}/5 - 0.2201 \times \text{age}/10 + 0.246738 \text{ (if male)} + 0.451013 \times \ln(\text{ACR}) + 3.11246)]}}$.

The 1-year risk equation and method for converting urine PCR to urine albumin-creatinine ratio (ACR) was obtained through personal communication with Dr Tangri. In the full AASK population, the C statistic for this equation was 0.9832 at 1 year and 0.8329 at 5 years.

Laboratory Measurements

As in previous studies, the AASK estimating equation was used to approximate measured GFR: eGFR $= 329 \times$ (serum creatinine)$^{-1.096} \times$ (age)$^{-0.294} \times$ (0.736 if female). Serum creatinine was measured twice at baseline, then at follow-up months 3 and 6, then every 6 months thereafter; all samples were auto-analyzed at the AASK Central Biochemistry Laboratory in the Department of Laboratory Medicine at the Cleveland Clinic. Urine protein and creatinine were measured using the pyrogallol red technique and the modified Jaffé reaction. PCR was dichotomized as ≤1 or >1 g/g, a higher threshold than previous AASK studies given the selection for more advanced CKD. Proteinuria also was expressed continuously as log-transformed ACR in order to use existing risk equations. PCR was converted to ACR by dividing by 0.0017566 if female and 0.002655 if male.[24]

Covariate and Outcome Ascertainment

Study visits were conducted at months 3 and 6 and every 6 months thereafter. Serum creatinine was measured at each visit, as was weight and blood pressure. Height at study enrollment was used in the calculation of body mass index. Hematocrit, urine protein, and urine creatinine were measured approximately yearly. Separately, for each of the 5 starting points, antecedent 3-year slope was estimated for each participant using linear regression of eGFR on time during all visits in the previous 3 years. Rapid progression was defined as an antecedent 3-year slope less than −5 mL/min per year. *APOL1* risk status was defined as the presence of 2 *APOL1* risk alleles, corresponding to the G1 (rs73885319 [leading to a serine to glycine substitution at amino acid 342] and rs60910145 [leading to an isoleucine to methionine substitution at amino acid 384]) and G2 (rs71785313) variants. Single-nucleotide polymorphisms were typed using ABI Taqman, and G1 or G2 homozygote status or G1/G2 compound heterozygous status were determined based on inferred haplotypes using PLINK.[27] All except 2 individuals had a posterior probability of 1 given the high linkage disequilibrium between the G1 and G2 alleles. The study outcome was ESRD, defined as self-reported initiation of dialysis therapy or transplantation. For the assessment of competing events, pre-ESRD death also was considered.

Statistical Analysis

Five different starting points were evaluated: eGFR of 30 mL/min/1.73 m^2, eGFR of 15 mL/min/1.73 m^2, and 1-year ESRD risk of 5%, 10%, and 20%. For each starting point, "baseline" was defined as the first visit in which a participant crossed the specified eGFR or 1-year ESRD risk threshold. For example, for analyses from eGFR of 30 mL/min/1.73 m^2, baseline characteristics represent the values at the earliest study visit in which eGFR was ≤30 mL/min/1.73 m^2. Because hematocrit and PCR were not measured at every study visit, missing values at the baseline visit were imputed with the most recent value obtained during a study visit in the previous 12 months. Participants were followed up from the qualifying visit date until ESRD, death, or end of study (June 30, 2007), whichever came first. Median times to ESRD or death were derived using Kaplan-Meier survival methods.

Competing-risk models were used to separately estimate the cumulative incidence of ESRD and pre-ESRD death, adjusting for