Development and Validation of a Model to Predict 5-Year Risk of Death without ESRD among Older Adults with CKD

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Abstract

Background and objectives CKD is associated with mortality. Accurate prediction tools for mortality may guide clinical decision-making, particularly among elderly persons with CKD.

Design, setting, participants, & measurements A prediction equation was developed for 5-year risk of mortality among participants with CKD in the Cardiovascular Health Study. Sixteen candidate predictor variables were explored, which included demographics, physical examination measures, comorbidity, medication use, and kidney function measures (eGFR calculated from serum creatinine and the CKD Epidemiology Collaboration equation and the urine albumin-to-creatinine ratio). Models were developed using Cox regression and evaluated using c statistics. A final parsimonious model was externally validated in an independent cohort of community-living elders with CKD in the Health, Aging, and Body Composition Study.

Results The development cohort included 828 participants who had a mean age of 80 (±5.6) years and an eGFR of 47 (±11) ml/min per 1.73 m^2, and median albumin-to-creatinine ratio of 13 (interquartile range 6–51) mg/g. The validation cohort included 789 participants who had a mean age of 74 (±2.8) years and an eGFR of 50 (±9) ml/min per 1.73 m^2, and median albumin-to-creatinine ratio of 13 (interquartile range 6–42) mg/g. The final model for 5-year mortality risk included age, sex, race, eGFR, urine albumin-to-creatinine ratio, smoking, diabetes mellitus, and history of heart failure and stroke (c statistic=0.72; 95% confidence interval, 0.68 to 0.74). When a point-based system was assigned for each of nine variables in the equation, the estimated risk of death within 5 years ranged from 3.8% among participants with the lowest scores to 83.6% among participants with nine points. The model performed fair in external validation (c statistic=0.69; 95% confidence interval, 0.64 to 0.74).

Conclusions A simple prediction tool using nine readily available clinical variables can assist in predicting 5-year mortality risk in elderly patients with CKD, which may be useful in counseling patients and guiding clinical decision making.

Clin J Am Soc Nephrol 10: 363–371, 2015. doi: 10.2215/CJN.04650514

Introduction

Patients with CKD are at high risk for death (1,2). Elderly patients with CKD comprise an especially vulnerable subgroup (3,4). Risk modification in elderly patients with CKD is often challenging because of the heterogeneity of disease and the competing risks of other adverse events, such as cardiovascular disease or progression to ESRD (1). However, it is well known that most elderly patients with CKD will die before developing these other complications.

CKD is associated with a high prevalence of traditional risk factors, such as advanced age, diabetes, and hypertension, that likely contribute to the high risk of mortality. However, the combined use of these risk factors to predict mortality among patients with CKD remains unknown. Currently, there are no widely used clinical prediction models to assess risk of mortality among elderly patients with CKD. If accurate and generalizable, a prediction model on the basis of widely available clinical variables could identify individuals at particularly high death risk, which may help prevent unnecessary and potentially harmful medical interventions that are focused on preventing or treating comorbidities that are less likely to occur than death itself. Therefore, in this study, we developed a tool using traditional risk factors to predict mortality among elderly persons with CKD in the Cardiovascular Health Study (CHS). To assess the performance of the equation in an independent sample, we subsequently externally validated the CKD death risk prediction equation in a separate cohort of community-living elders with CKD in the Health, Aging, and Body Composition (Health ABC) Study.

Materials and Methods

Study Populations

Development Cohort. The CHS was the development cohort for this study. The CHS is a prospective, longitudinal study of older community-dwelling adults. The study methods have been previously described (5). Participants were recruited from Medicare eligibility lists at four locations: Forsyth County, North Carolina; Sacramento County, Calfornia; Washington County, Maryland; and Pittsburgh, Pennsylvania. To be eligible, participants were required to be community dwelling, age 65 years or older, expected to remain in the area for 3 years after recruitment, not receiving active treatment for cancer, and able to give informed consent without a proxy. The original cohort was recruited in 1989 through 1990, and a second cohort of 687 black individuals was recruited in 1992 through 1993, resulting in 5888 participants, all of whom provided informed consent.

We selected the 1996/1997 study visit as our baseline visit for this study. This visit was selected, because it was the first visit at which morning urine samples were collected and measured for urine albumin-to-creatinine ratios (UACRs). There were 3406 individuals who participated in the 1996/1997 study visit; of those, 836 individuals had eGFR$<$60 ml/min per 1.73 m^2 (on the basis of serum creatinine and the CKD Epidemiology Collaboration [CKD-EPI] equation) (6). Of these 836 individuals, we excluded eight individuals with missing covariates, which yielded a sample size of 828 participants with CKD in the CHS.

Validation Cohort. The Health ABC Study enrolled 3075 well functioning men and women 70–79 years of age recruited from a sample of Medicare beneficiaries at two clinical sites (Pittsburgh, Pennsylvania, and Memphis, Tennessee) at the baseline study visit (April of 1997 to June of 1998). To be eligible, participants reported no difficulty in walking one quarter of a mile, climbing 10 steps, or performing basic activities of daily living. Venous blood samples were obtained after overnight (8-hour) fasts and stored at −70°C. Participants underwent a daylong evaluation that included medical history and physical activity assessment, medication use, and physical examination. All participants provided written informed consent, and the study was approved by the institutional review boards at the University of Pittsburgh and the University of Tennessee Health Sciences Center. Among 3075 eligible participants, 49 individuals had missing UACR, 13 individuals had missing creatinine, 2170 individuals had an eGFR$>$60 ml/min per 1.73 m^2 by the creatinine-based CKD-EPI equation, and 54 individuals had missing covariate data, leaving 789 participants with CKD in the Health ABC Study for our validation analysis.

Candidate Predictor Variables

Sixteen candidate predictor variables were considered in this analysis on the basis of previous literature and clinical acumen, and availability in both the development and validation cohorts (7–9). *A priori*, we selected variables that are commonly available in routine clinical practice and large administrative datasets because we believe that the resulting prediction equation might have clinical and research uses in these settings; thus, a parsimonious list was considered an advantage for external use. The candidate variables included demographic variables (age, sex, and race), comorbid diseases (history of coronary heart disease [CHD], heart failure [HF], stroke, hypertension, or diabetes mellitus), tobacco use (never, former, or current), physical examination measures (systolic BP and body mass index in kilograms per meter^2), and laboratory values (eGFR [6], UACR, total cholesterol, and serum albumin). Although not available in the Health ABC Study, we also assessed change in eGFR over 4 years in the CHS, because a trajectory of change in kidney function is often used clinically to assess rate of progression of kidney disease and might also predict death (10). Medication use (antihypertensive and lipid-lowering medications) was determined by participant pill bottles and recorded by study personnel.

Development Cohort. In the CHS, comorbid diseases were determined by self-report. Diabetes was defined as fasting glucose ≥126 mg/dl or use of oral hypoglycemic medications or insulin. A random morning urine sample was obtained and measured for urine albumin by rate nephelometry and creatinine using a Kodak Ektachem 700 Analyzer (Kodak, Rochester, New York). UACR was calculated in micrograms per gram.

Validation Cohort. In the Health ABC Study, diabetes was defined by history of physician's diagnosis, use of hypoglycemic medications, fasting glucose level ≥126 mg/dl, or 2-hour postchallenge plasma glucose level ≥200 mg/dl. Samples were drawn after an 8-hour fast and stored at −70°C until they were assayed at the study core laboratory. The urine albumin assay was on the basis of a particle-enhanced turbidimetric inhibition immunoassay adapted to a clinical chemistry system, which allows direct quantitation of albumin in urine samples (Siemens, Newark, Delaware). Urine creatinine was measured by a modified Jaffe method on a clinical chemistry analyzer (Siemens). Both cohorts used the same central laboratory at the University of Vermont (Burlington, Vermont).

Outcome

The primary outcome was all-cause mortality within 5 years without ESRD or all-cause mortality within 5 years without ESRD. Date of ESRD was determined by linkage to the United States Renal Data System. Participants were censored at ESRD (defined as receipt of dialysis or a kidney transplant) or end of the study period (5 years from inclusion into the study). There was no loss to follow-up in either cohort because of rigorous ascertainment of mortality for all study participants.

Development Cohort. Among participants in the CHS, deaths were identified by review of obituaries, medical records, death certificates, and the Centers for Medicare and Medicaid Services Healthcare use database for hospitalizations and from household contacts (11).

Validation Cohort. Among participants in the Health ABC Study, death was determined within 5 years of study entry (12). Dates of death were obtained from death certificates, medical records, death certificates, proxy information, and autopsy reports when performed.

Statistical Analyses

Model Development in the CHS. We began by comparing baseline characteristics of participants in the development and validation cohorts. The association of candidate variables with mortality was assessed in univariate Cox models using bootstrap estimation (1000 replications; resampling with replacement). The functional forms of continuous predictors

(linear versus nonlinear relations with mortality) were evaluated using cubic spline functions. Only systolic blood pressure was modeled in categories (<110, 110–139, and ≥140 mmHg) given the nonlinear association with mortality. For the development cohort, we had 828 participants with CKD, 283 deaths, and 20 degrees of freedom, which were sufficient to conduct the proposed analyses (13). All terms with a *P* value ≤0.10 (Wald chi-squared test) were considered for inclusion in multivariable models. To identify independent predictors of mortality, we used a backward elimination approach. The threshold to retain a term in the model was set to a *P* value ≤0.10 (Wald chi-squared test). We used bootstrap estimation to obtain bias-corrected coefficients and confidence intervals (14). The goodness of fit of the final model was evaluated by Hosmer–Lemeshow chi square (15). The bias-corrected coefficients of the final model formed the basis for the CKD mortality risk score.

In secondary analyses, we included the variable of eGFR change over 4 years as a candidate predictor in our model. This was a secondary analysis, because this variable was not available in our validation cohort and therefore, would not be able to be externally validated if it was retained in the final multivariable model.

We used two measures of performance: the c statistic and the slope of the linear predictor. These were validated using 1000 bootstrap samples. The c statistic is a measure of discrimination of the model, showing the ability to distinguish high- from low-risk participants with values ranging from 0.5 (indicating random prediction) to 1.0 (perfect prediction). The slope of the linear predictor is a measure of model calibration, thus showing how closely predicted outcomes agree with actual outcomes. Perfect calibration is 1 and becomes worse as the value deviates from 1; values <20 generally indicate good calibration (16). This calibration value takes into account the sample size, number and time to events, and predicted probabilities. Validating the slope of the linear predictor by bootstrapping provides a means to moderate absolute predictions by recalibrating the linear predictor using the optimism-corrected slope known as shrinkage (17).

Generation of the Point-Scoring Scheme. To obtain more conservative estimates, we recalibrated the linear predictor of the model using the optimism-corrected slope (slope shrinkage factor) to get the 5-year mortality risk predictions. To increase the usefulness of the risk algorithm in clinical practice, we generated a simple scoring scheme similar to the one used for the Framingham Risk Score (18). Each risk factor was divided into categories and assigned an appropriate number of points. A regression equation was then calculated between the logarithm of global risk as calculated by use of the Cox model in conjunction with the survival curves and

Table 1. Baseline characteristics of development and validation cohorts for predicting 5-year mortality risk in community-dwelling adults with renal disease

Participant Characteristic	Cardiovascular Health Study	Health, Aging, and Body Composition Study	*P* Value
Number of participants	828	789	
Demographics			
Age (yr)±SD	79.9±5.6	74.1±2.8	<0.001
Women, *n*	459 (55%)	394 (50%)	0.04
Black race, *n*	146 (18%)	287 (36%)	<0.001
Prevalent cardiovascular disease, *n*			
History of coronary heart disease	273 (33%)	194 (25%)	<0.001
History of heart failure	144 (17%)	41 (5%)	<0.001
History of stroke	79 (10%)	86 (11%)	0.50
History of any cardiovascular disease	349 (42%)	247 (31%)	<0.001
Cardiovascular disease risk factors			
Hypertension, *n*	597 (72%)	580 (74%)	0.40
Systolic blood pressure (mmHg)±SD	138±22	138±22	>0.99
Use of hypertension medications, *n*	615 (74%)	502 (64%)	<0.001
Diabetes, *n*	140 (17%)	185 (23%)	0.003
Smoking, *n*			
Never	391 (47%)	364 (46%)	0.70
Former	385 (46%)	365 (46%)	>0.99
Current	52 (6%)	60 (8%)	0.10
Body mass index (kg/m^2)±SD	27.1±4.7	27.8±4.7	0.003
Weight (lb)±SD	160.4±31.5	169.4±32.3	<0.001
Total cholesterol (mg/dl)±SD	203±43	204±41	0.60
Serum albumin (g/dl)±SD	3.83±0.30	3.99±0.33	<0.001
Serum albumin ≤3.70 g/dl, *n*	259 (31%)	174 (22%)	<0.001
Use of lipid-lowering medications, *n*	115 (14%)	133 (17%)	0.10
Kidney function			
eGFR (ml/min per 1.73 m^2)±SD	47±11	50±9	<0.001
Urine albumin-to-creatinine ratio (mg/g), median [interquartile range]	13 [6–51]	13 [6–42]	0.02
Urine albumin-to-creatinine ratio>30 mg/g, *n*	253 (31%)	199 (25%)	<0.01

the categories of each risk factor. The coefficients calculated in this manner were then standardized and rounded to the nearest integer. For each level of score, the 5-year mortality risk was calculated. We further divided the score into quartiles of risk categories (≤10%, 11%–15%, 16%–25%, and >25%) and plotted the Kaplan–Meier curve for these risk groups.

Model Validation in the Health ABC Study. The performance of the prediction equation created in the CHS was assessed using discrimination and calibration metrics in the Health ABC Study. The participants in the Health ABC Study were divided into deciles according to the predicted 5-year mortality risk using the model coefficients that we developed in the CHS. Scatter plots were generated to show predicted and actual event rates for each decile, where the predicted event rate was calculated by summing the CHS predicted risk within the specific decile. A Hosmer–Lemeshow chi-squared test was used to compare the differences between predicted and actual event rates (16). Similar to the development cohort, the point scale was applied to the validation cohort, and the mortality risk for each point total was determined.

Sensitivity Analyses. We performed a *post hoc* analysis to determine if our prediction equation performed well in predicting 2-year mortality. Because of limitations in power, the development and validation cohorts were combined for this analysis.

All analyses were conducted using SPSS statistical software (version 16.0.2; SPSS Inc., Chicago, IL) and R, version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) using the design library provided by Frank E. Harrell. P values ≤0.10 were considered statistically significant for all analyses.

Results

Baseline Characteristics of Study Participants

Compared with 789 participants in the validation cohort (the Health ABC Study), participants in the development

Table 2. Univariate determinants of 5-year mortality in participants with CKD in the Cardiovascular Health Study (*n*=828)

Variable	No. of Deaths	No. at Risk	Mortality Rate (%/yr)	Unadjusted Hazard Ratio (95% Confidence Interval)	*P* Value
Age (per SD=5-yr increase)	283	828	8.13	1.53 (1.38 to 1.69)	<0.001
Sex					
Women	132	459	6.59	1.00	
Men	151	369	10.22	1.58 (1.25 to 1.99)	<0.001
Race					
White	242	682	8.49	1.32 (0.95 to 1.83)	0.10
African American	41	146	6.51	1.00	
Kidney function					
eGFR creatinine (per SD=11 ml/min per 1.73 m^2 lower)	283	828	8.13	1.40 (1.27 to 1.55)	<0.001
Urine albumin-to-creatinine ratio (mg/g)					
≤30	575	152	6.03	1.00	
>30	253	131	13.62	2.33 (1.84 to 2.94)	<0.001
Body mass index (kg/m^2)					
≤20	17	34	13.59	1.42 (0.85 to 2.37)	0.20
20.1–24.9	102	257	9.81	1.00	
25.0–29.9	105	354	6.91	0.70 (0.53 to 0.92)	<0.01
≥30.0	59	183	7.41	0.75 (0.54 to 1.03)	0.08
Systolic BP (mmHg)					
<110	67	29	11.06	1.00	
110–139	405	128	7.45	0.67 (0.45 to 0.99)	0.05
≥140	356	126	8.40	0.75 (0.50 to 1.13)	0.20
Hypertension medications	219	615	8.51	1.21 (0.91 to 1.60)	0.20
Diabetes	68	140	12.69	1.77 (1.35 to 2.33)	<0.001
Smoking					
Never	112	391	6.67	1.00	
Former	148	385	9.31	1.41 (1.10 to 1.80)	<0.01
Current	23	52	10.87	1.65 (1.05 to 2.58)	0.03
Cholesterol (per SD=43 mg/dl higher)	283	828	8.13	0.85 (0.73 to 0.96)	0.01
Lipid-lowering medications	34	115	6.78	0.81 (0.56 to 1.15)	0.20
Prevalent coronary heart disease	117	273	10.81	1.58 (1.25 to 2.01)	<0.001
Prevalent heart failure	92	144	19.23	3.19 (2.49 to 4.09)	<0.001
Prevalent stroke	44	79	15.40	2.12 (1.54 to 2.93)	<0.001
Serum albumin (g/dl)					
>3.70	182	569	7.47	1.00	
≤3.70	101	259	9.66	1.31 (1.02 to 1.67)	0.03
Change in eGFR (ml/min per 1.73 m^2 change from years 5 to 9)	283	828	8.13	1.08 (0.96 to 1.21)	0.20

cohort (the CHS; n=828) were older; more likely to be women and white; more likely to have prevalent CHD, HF, and stroke; and more likely to have lower eGFR and higher UACR (Table 1).

Model Development in the CHS

Over 5 years, there were 283 deaths (34%) among the 828 participants in the CHS. Among the same individuals and time-frame, there were 32 incident ESRD events, which was a censoring event in this analysis. In univariate analyses, participants who died within 5 years were more likely to be older; be men; be white; have lower eGFR; have higher UACR; have lower body mass index; have diabetes; use tobacco; have lower cholesterol; have a history of CHD, stroke, or HF; and have lower serum albumin (Table 2).

In a final multivariable model, older age, men, white race, lower eGFR, high UACR, diabetes, tobacco use, and history of HF and stroke were independently and significantly associated with 5-year mortality and thus, retained in the final model (Table 3). Prevalent HF and current smoking carried the most weight in the predictive equation. The β-coefficients, hazard ratios, and final multivariable model derived in the CHS are shown in Table 3. The c statistic for the model was 0.72 (95% confidence interval, 0.68 to 0.74), with a calibration value of 7.80 (P=0.50).

In secondary analyses, we also included change in eGFR over 4 years before baseline as a candidate predictor variable. Among participants in the CHS, the mean eGFR change was a 9-ml/min per 1.73 m^2 decrease over 4 years. However, eGFR change was not associated with mortality in univariate analyses (Table 2). Thus, this variable was not retained in the final model. The total observed number of deaths in the CHS was 283, and the overall number of predicted deaths was 283.1. The predicted versus observed mortality rates were relatively well matched (Figure 1A).

When a point-based system was assigned for each of nine variables in the equation (Table 4), the estimated risk of death within 5 years ranged from 3.8% among participants with the lowest scores to 93.7% in participants with ≥10 points (Table 5). We further divided the score into quartiles of risk categories (≤10%, 11%–15%, 16%–25%, and >25%) and plotted the Kaplan–Meier curves for these risk groups, which show that the cumulative incidence of death was greater in the higher risk quartiles and seemed to remain fairly consistent across the 5-year follow-up period (Figure 2A).

Validation in the Health ABC Study

Among 789 participants with CKD in the Health ABC Study validation cohort, there were 125 deaths over 5 years. When the nine-variable equation that was developed in the CHS was applied to the Health ABC Study, there were 125 predicted deaths. The c statistic was 0.69 (95% confidence interval, 0.64 to 0.74), and the calibration value was 3.96 (P=0.90). Similar to the development cohort, the predicted versus observed rates of death were well matched in the Health ABC Study (Figure 1B). We also applied the point scale to the validation cohort (Table 5). Kaplan–Meier curves by quartiles of risk categories in the Health ABC Study revealed greater cumulative incidence of death in the highest risk categories, which was particularly evident after longer follow-up (Figure 2B).

Sensitivity Analyses

In a sensitivity analysis, we combined the development and validation cohorts to determine if our prediction equation performed well in predicting 2-year mortality. Among 1617 participants in both cohorts, there were 130 deaths within 2 years. The c statistic for the final model, which included all nine variables, was 0.77 (95% confidence interval, 0.71 to 0.80).

Table 3. Final multivariable model for 5-year risk of mortality for participants with CKD in the Cardiovascular Health Study

Covariate	Bias-Corrected Coefficient	Bias-Corrected Hazard Ratio (95% Confidence Interval)	P Value
Age (per 5 yr older)	0.43	1.54 (1.35 to 1.75)	0.001
Men	0.20	1.22 (0.95 to 1.63)	0.10
White	0.29	1.33 (0.96 to 1.98)	0.10
eGFR creatinine (per SD=11 ml/min per 1.73 m^2)	0.16	1.18 (1.03 to 1.35)	0.01
Urine albumin-to-creatinine ratio (mg/g)	0.48		0.001
≤30		1.00 (reference)	
>30		1.61 (1.18 to 2.17)	
Diabetes	0.41	1.51 (1.11 to 2.01)	0.001
Smoking			<0.01
Never		1.00 (reference)	
Former	0.32	1.38 (1.05 to 1.80)	
Current	0.77	2.16 (1.33 to 3.46)	
Prevalent heart failure	0.85	2.33 (1.70 to 3.25)	0.001
Prevalent stroke	0.35	1.42 (0.93 to 2.13)	0.07

The Cardiovascular Health Study equation: 5-year mortality risk prediction equation: $1-0.8307127\exp^{(\Sigma\beta x-6.915019)}$, where β is the regression coefficient, and x is the level for each risk factor. To compute 1-year risk of mortality, the formula $\ln(1-0.8307127\exp^{(\Sigma\beta x-6.915019)})/5$; c statistic=0.72 (95% confidence interval, 0.68 to 0.74) can be used. Calibration value (using the linear predictor)=7.80 (P=0.40).

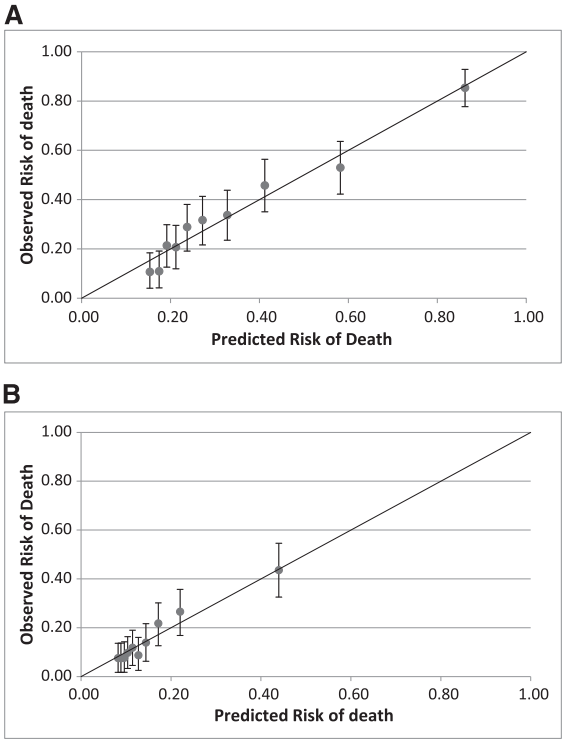

Figure 1. | The predicted risk of death using the CKD mortality model versus the observed risk of death were well calibrated in the Cardiovascular Health Study and the Health ABC Study. (A) Calibration of the Cardiovascular Health Study (CHS) CKD mortality model. Observed risks versus predicted risks of death by decile of predicted risks of death (with 95% confidence intervals) are shown. The model was well calibrated, with a Hosmer–Lemeshow chi square of 7.80 (P=0.40). (B) Calibration in the Health, Aging, and Body Composition Study of the CKD mortality equation developed in the CHS. Observed risks versus predicted risks of death by decile of predicted risks of death (with 95% confidence intervals) are shown. The model was well calibrated, with a Hosmer–Lemeshow chi square of 3.96 (P=0.90).

Discussion

We developed and externally validated a new prediction tool for mortality risk among elderly persons with CKD using nine readily available clinical variables, which included demographic factors, measures of kidney function, traditional cardiovascular risk factors, and comorbid diseases. The model had fair discrimination when externally validated in an independent sample in the Health ABC Study. We believe that this prediction tool has clinical applicability to help identify older patients with CKD at high risk of death within 5 years.

Our prediction model for mortality included nine readily available clinical variables, including demographic factors, measures of kidney function, traditional cardiovascular risk factors, and comorbid diseases. Rapid decline in kidney function has been found to be associated with cardiovascular events and death in the elderly (10,19), but it was not statistically significant in our multivariable regression models for mortality and thus, was not retained in the final model. Serum albumin was shown to be predictive of 5-year mortality in a previous analysis in the CHS that included participants with and without CKD (20); however, it did not improve prediction of death in our analysis, which was limited to those with CKD. The newly developed model had comparable discrimination and prediction in our validation cohort.

There has been considerable interest in the development of prediction equations for adverse outcomes among patients with CKD. A recent meta-analysis identified eight studies that have developed equations to predict risk of progression to ESRD, three studies that have developed equations to predict cardiovascular disease, and five studies that have developed equations to predict death (21). Of five studies focused on death prediction, one exclusively evaluated patients with biopsy-proven IgA nephropathy (22), and two studies focused only on patients with diabetes (23,24). A study of patients with CKD with mean age of 74 years from Kaiser Permanente Northwest found that demographics, eGFR, and diabetes predicted death, similar to our study. The c statistic for their prediction model was similar to ours in the development dataset (0.70 versus 0.72 in our study). However, this study did not have measures of albuminuria available and did not validate the prediction model in an external study population (25). Another analysis of 382 middle-aged patients with CKD studied 44 characteristics, including many novel biomarkers (26). Age, N-terminal pro-brain natriuretic peptide, smoking, and troponin T predicted death with excellent discrimination (c statistic=0.82), and this model performed well in an external cohort (26). In contrast to our study, this study evaluated a smaller middle-aged study population from a single center. Our prediction model builds on these prior studies by developing a model to predict death specifically in elderly patients with CKD, a high-risk and growing population with unique clinical considerations.

The burden of CKD is particularly high in the elderly, likely because of a high burden of comorbid diseases and loss of kidney function related to aging and longer-term exposure to CKD risk factors over the life course. It is well known that the competing risk of death versus ESRD is high among patients with CKD (1). This is particularly relevant to elderly patients, who often have slower progression of kidney disease and a higher risk of death. The ability to quantify risks of death in elderly patients with CKD may help guide immediate clinical management. For example, it may help clinicians identify patients less likely to benefit from surgical procedures to prepare for dialysis (*e.g.*, vascular access placement). It may also reduce aggressive pharmaceutical management with medications, such as renin-angiotensin-aldosterone-system inhibitors, which commonly cause hyperkalemia, hypotension, and frequent monitoring with blood tests, all of which may be cumbersome to the elderly patient with CKD. Last, it may help identify elderly patients with CKD who may benefit from closer surveillance or targeted preventive interventions, which may be an application of our prediction equation in administrative databases in addition to the clinic with individual patients. Compared with previous studies, we specifically focused on identification of a predictive model populated by a parsimonious list of variables that are readily available in most contemporary medical practices, thus potentially broadening the clinical applicability of the prediction equation.

Strengths of this study include its evaluation of a relatively large population of community-living elderly individuals

Table 4. Points associated with each risk factor in the CKD mortality equation derived in the Cardiovascular Health Study

Risk Factor Categories	Points
Age (yr)	
70–74	0
75–79	1
80–84	2
≥85	4
Sex	
Women	0
Men	1
Race	
Black	0
White	1
eGFR creatinine (ml/min per 1.73 m^2)	
50–59	0
40–49	1
30–39	2
<30	4
Urine albumin-to-creatinine ratio≥30 mg/g	
No	0
Yes	1
Diabetes	
No	0
Yes	1
Smoking	
Never	0
Former	1
Current	2
Prevalent heart failure	
No	0
Yes	2
Prevalent stroke	
No	0
Yes	1

with CKD recruited from across the United States. Consistent with recent recommendations on developing prediction models, we had appropriate sample sizes with sufficient numbers of events to develop our prediction model, we only included complete case data, we explored nonlinear relationships between our predictors and outcome using cubic splines, and we externally validated our prediction equation in an independent sample of elderly participants with CKD (27). We studied a broad range of candidate predictors. As such, our findings allow us to move forward a prediction equation that could be implemented using standard clinical variables.

Our study has important limitations. We were unable to confirm the chronicity of CKD because of the relatively infrequent study visits. The participants had relatively moderate CKD severity at baseline, with low levels of proteinuria. Although this pattern of CKD is common in elderly persons, it is possible that predictors of mortality may differ in patients with more advanced CKD or more severe albuminuria. We had few patients with ESRD and therefore, were not able to examine competing risk of ESRD in our analysis. In evaluating comorbidity, we used a simplistic yes or no approach, which may oversimplify the effect of that disease on risk of death. Evaluation of severity may have improved model performance but limited the use of the equation in clinical practice. Our study population may not be completely generalizable to all elderly patients with CKD because of specific exclusion criteria for each cohort (for example, the Health ABC Study excluded participants with impaired activities of daily living). To develop our prediction model, we used clinical acumen to select candidate variables and then statistical significance to determine which variables were included in the final model. We recognize that relying on statistical significance may yield different accuracy of the final model compared with an approach where only clinical acumen is used for variable selection. However, when we tested this alternative approach, we found no difference in the discrimination of the models (results not shown). The point scale that was developed may be limited in calibration and may not predict death with the same accuracy as the regression equation. Even with this limitation, we feel that the point score had value in providing a quick and easy tool that could readily be applied clinically. Finally, the CHS and the Health ABC Study recruited participants >10 years ago. There may be secular trends in mortality, which may also limit the generalizability of our study.

In conclusion, we have developed and externally validated a simple equation to predict death among elderly patients with CKD. This tool may prove useful to clinicians weighing decisions regarding preparation for ESRD and intensity of CKD therapy against the high competing risks of death.

Table 5. Risk associated with the point totals using the risk score for 5-year mortality in the development and validation cohorts

Point Total	Estimate of Risk (%)	Cardiovascular Health Study		Health, Aging, and Body Composition Study	
		N (%)	No. of Deaths (%)	*N* (%)	No. of Deaths (%)
0	3.87	2 (0.2)	0 (0)	26 (3.3)	1 (3.8)
1	5.85	23 (2.8)	2 (8.7)	91 (11.5)	7 (7.7)
2	8.82	67 (8.1)	8 (11.9)	106 (13.4)	11 (10.4)
3	13.16	127 (15.3)	20 (15.7)	150 (19.0)	12 (8.0)
4	19.42	146 (17.6)	30 (20.5)	138 (17.5)	25 (18.1)
5	28.13	138 (16.7)	47 (34.1)	129 (16.3)	17 (13.2)
6	39.66	105 (12.7)	42 (40.0)	76 (9.6)	22 (28.9)
7	53.82	87 (10.5)	43 (49.4)	29 (3.7)	9 (31.0)
8	69.33	46 (5.6)	23 (50.0)	24 (3.0)	11 (45.8)
9	83.60	39 (4.7)	29 (74.4)	14 (1.8)	6 (42.9)
≥10	93.70	48 (5.8)	39 (81.3)	6 (0.7)	4 (80.0)

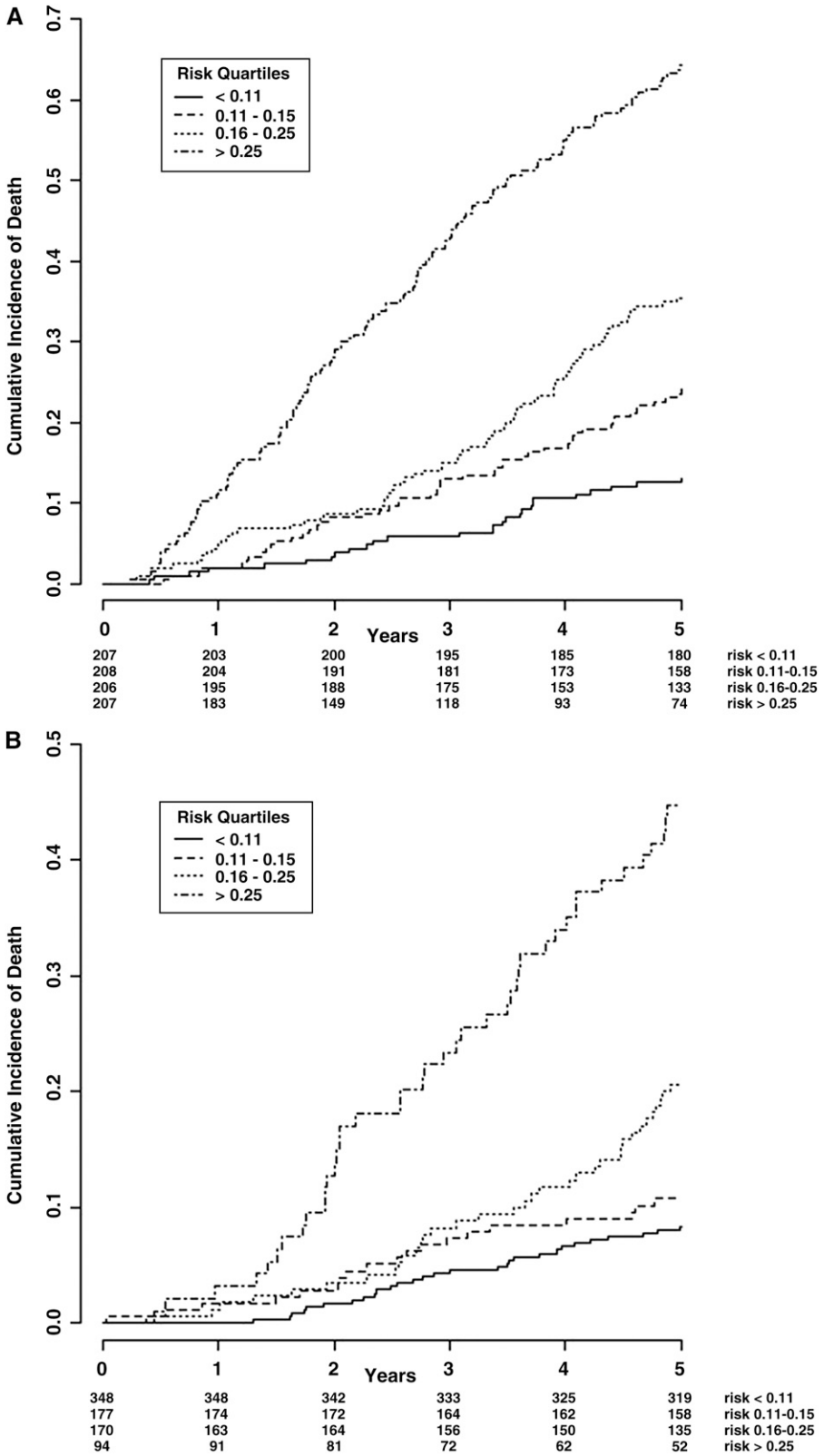

Figure 2. | Cumulative incidence for mortality greater in the highest quartile of risk among participants with CKD in the the Cardiovascular Health Study and Health ABC Study. (A) Kaplan–Meier curves for mortality for participants with CKD in the Cardiovascular Health Study (CHS) on the basis of quartiles of risk score in the CHS. (B) Kaplan–Meier curves for mortality for participants with CKD in the Health, Aging, and Body Composition Study on the basis of quartiles of risk from the CHS score.

Acknowledgments

This work was supported by National Institute for Diabetes Digestive and Kidney Diseases Grant K23DK088865 (to N.B.), National Institutes on Aging (NIA) Grant R01AG027002 (to M.J.S.), and American Heart Association Established Investigator Award EIA18560026 (to J.H.I.). The Cardiovascular Health Study (CHS) research was supported by National Heart, Lung, and Blood Institute Contracts HHSN268201200036C, HHSN268200800007C, N01-HC55222, N01-HC85079, N01-HC85080, N01-HC85081, N01-HC85082, N01-HC85083, and N01-HC85086 and Grant HL080295, with additional contribution from the National Institute of Neurological Disorders and Stroke; additional support was provided by NIA Grant AG023629. The Health, Aging, and Body Composition Study research was supported by NIA Contracts N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106; NIA Grant R01-AG028050; National Institute of Nursing Research (NINR) Grant R01-NR012459; and in part, the Intramural Research Program of the National Institutes of Health, NIA.

A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.

Disclosures

None.

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Received: May 12, 2014 **Accepted:** November 26, 2014

Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, "Predicting Death without Dialysis in Elderly Patients with CKD," on pages 341–343.