AJKD

Original Investigation

A Meta-analysis of the Association of Estimated GFR, Albuminuria, Age, Race, and Sex With Acute Kidney Injury

*Morgan E. Grams, MD, PhD,[1,2] Yingying Sang, MS,[2] Shoshana H. Ballew, PhD,[2] Ron T. Gansevoort, MD, PhD,[3] Heejin Kimm, MD, PhD,[4] Csaba P. Kovesdy, MD,[5] David Naimark, MD, MSc,[6] Cecilia Oien, MD, PhD,[7] David H. Smith, RPh, PhD,[8] Josef Coresh, MD, PhD,[2] Mark J. Sarnak, MD, MS,[9] Benedicte Stengel, MD,[10] and Marcello Tonelli, MD, SM,[11] on behalf of the CKD Prognosis Consortium**

Background: Acute kidney injury (AKI) is a serious global public health problem. We aimed to quantify the risk of AKI associated with estimated glomerular filtration rate (eGFR), albuminuria (albumin-creatinine ratio [ACR]), age, sex, and race (African American and white).

Study Design: Collaborative meta-analysis.

Setting & Population: 8 general-population cohorts (1,285,049 participants) and 5 chronic kidney disease (CKD) cohorts (79,519 participants).

Selection Criteria for Studies: Available eGFR, ACR, and 50 or more AKI events.

Predictors: Age, sex, race, eGFR, urine ACR, and interactions.

Outcome: Hospitalized with or for AKI, using Cox proportional hazards models to estimate HRs of AKI and random-effects meta-analysis to pool results.

Results: 16,480 (1.3%) general-population cohort participants had AKI over a mean follow-up of 4 years; 2,087 (2.6%) CKD participants had AKI over a mean follow-up of 1 year. Lower eGFR and higher ACR were strongly associated with AKI. Compared with eGFR of 80 mL/min/1.73 m^2, the adjusted HR of AKI at eGFR of 45 mL/min/1.73 m^2 was 3.35 (95% CI, 2.75-4.07). Compared with ACR of 5 mg/g, the risk of AKI at ACR of 300 mg/g was 2.73 (95% CI, 2.18-3.43). Older age was associated with higher risk of AKI, but this effect was attenuated with lower eGFR or higher ACR. Male sex was associated with higher risk of AKI, with a slight attenuation in lower eGFR but not in higher ACR. African Americans had higher AKI risk at higher levels of eGFR and most levels of ACR.

Limitations: Only 2 general-population cohorts could contribute to analyses by race; AKI identified by diagnostic code.

Conclusions: Reduced eGFR and increased ACR are consistent strong risk factors for AKI, whereas associations of AKI with age, sex, and race may be weaker in more advanced stages of CKD.

Am J Kidney Dis. ■(■):■-■.

INDEX WORDS: Estimated glomerular filtration rate (eGFR); renal function; albuminuria; albumin-creatinine ratio (ACR); proteinuria; age; race/ethnicity; sex; acute kidney injury (AKI); acute renal failure (ARF); Chronic Kidney Disease Prognosis Consortium; meta-analysis.

Acute kidney injury (AKI) is increasingly recognized as a serious problem in global public health.[1] Although estimates of AKI incidence in the general population are sparse, AKI occurs in 3.2% to 9.6% of hospital admissions[2,3] and 2.1% to 22.1% of prevalent intensive care unit patients[4] worldwide. Furthermore, AKI is associated with substantial morbidity, including prolonged hospital stay, end-stage renal disease, earlier stages of chronic kidney disease (CKD), and short- and long-term mortality.[3,5,6]

From the [1]Department of Medicine, Division of Nephrology, Johns Hopkins University School of Medicine; [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [3]Department of Nephrology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; [4]Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Korea; [5]Memphis Veterans Affairs Medical Center, Memphis, TN; [6]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; [7]Norwegian University of Science and Technology and St Olavs University Hospital, Trondheim, Norway; [8]Center for Health Research, Kaiser Permanente Northwest, Portland, OR; [9]Division of Nephrology, Tufts Medical Center, Boston, MA; [10]Inserm U1018, CESP Centre for Research in Epidemiology and Population Health and UMRS 1018, Paris-Sud University, Villejuif, France; and [11]Department of Medicine, University of Calgary, Calgary, Alberta, Canada.

[*]A list of the CKD Prognosis Consortium investigators and collaborators appears in the Acknowledgements.

Received October 24, 2014. Accepted in revised form February 26, 2015.

Because this article was considered jointly with an article for which an author is an editor of AJKD, the peer-review and decision-making processes were handled entirely by an Associate Editor (Beth Piraino, MD) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Information for Authors & Editorial Policies.

Address correspondence to Chronic Kidney Disease Prognosis Consortium Data Coordinating Center, Principal Investigator, Josef Coresh, MD, PhD, 2024 E Monument St, Baltimore, MD 21287. E-mail: ckdpc@jhmi.edu

0272-6386

http://dx.doi.org/10.1053/j.ajkd.2015.02.337

Certain patient characteristics may predispose to AKI. CKD, assessed as decreased estimated glomerular filtration rate (eGFR) or elevated albuminuria, has been linked to increased AKI risk.[7-10] Similarly, older age, male sex, and African American race have been associated with higher risk of AKI.[11-13] The generalizability of existing studies investigating demographic risk factors is limited, with most estimates derived in single cohorts. In addition, little attention has been paid to how demographic associations may vary over the spectrum of kidney function. Thus, the objectives of this study were to evaluate the associations of eGFR and albuminuria with AKI in a large global consortium of studies, as well as to investigate the relative importance of age, sex, and race across the full range of eGFR and albuminuria.

METHODS

Design Overview

Study data were obtained by the CKD Prognosis Consortium (CKD-PC) for meta-analysis as previously described.[10,14-17] Cohorts with baseline measurements of eGFR and albuminuria, at least 1,000 participants (not applied to cohorts preferentially enrolling persons with eGFRs < 60 mL/min/1.73 m^2), and at least 50 AKI events were eligible for inclusion. This study was approved for use of deidentified data by the Institutional Review Board (IRB) at the Johns Hopkins University Bloomberg School of Public Health (IRB number: 3324).

Settings and Participants

Thirteen studies met eligibility criteria. All cohorts were included in analyses of AKI incidence and the risk associated with eGFR, but only those with measured risk factors or populations relevant for the comparison of interest were included in analyses of albumin-creatinine ratio (ACR), age, sex, and race (eg, studies measuring proteinuria by dipstick were not included in continuous analyses of ACR, and the all-male Uppsala Longitudinal Study of Adult Men [ULSAM] was not included in the analysis by sex). For the present study, only participants with baseline eGFR > 15 mL/min/1.73 m^2 were included, and participating studies were categorized as either general-population or CKD cohorts, reflecting the distribution of eGFR and ACR.

Interventions

eGFR was calculated using creatinine concentrations (standardized when possible to isotope-dilution mass spectrometry) and the 2009 CKD Epidemiology Collaboration (CKD-EPI) creatinine equation.[18] The preferred measure of albuminuria was urine ACR; however, cohorts with quantitative dipstick protein were also included in analyses of eGFR, adjusting for ordinal category of dipstick results. In categorical analyses, dipstick test results of negative, trace, 1+, and ≥2+ were considered equivalent to ACR < 10, 10 to 29, 30 to 299, and ≥300 mg/g, respectively,[19,20] and the groups of ACR < 30, 30 to 299, and ≥300 mg/g were referred to as no albuminuria, moderately increased albuminuria, and severely increased albuminuria.[21] Age, sex, and race were self-reported, with the former categorized as 18 to 54, 55 to 64, 65 to 74, and 75 years or older in interaction analysis, and the latter categorized as African American and non–African American (95% of non–African American participants were white) when used as a covariate in adjustment and African American and white when used as a covariate in the interaction analysis.

Outcomes and Follow-up

The primary outcome was diagnostic code–defined AKI, determined as an *International Classification of Disease, Ninth Revision, Clinical Modification* code of 584.x or *International Classification of Disease, Tenth Revision, Clinical Modification* code of N17.x associated with a hospitalization. These codes have been validated previously in the United States, Israel, and Canada, with lower sensitivity (range, 17%-80%) but high specificity (range, 96%-100%).[22-24] Sensitivity was generally higher for more severe disease.[25] Follow-up was censored at the development of end-stage renal disease, death, or loss to follow-up.

Statistical Analysis

Analyses were performed by 2-stage meta-analysis. At the first stage, each study was analyzed individually, using all participants 18 years or older with baseline eGFR and albuminuria. Missing values for covariates other than age, sex, and race were estimated using mean imputation. Variables missing in >50% of the cohort were not included as covariates (Item S1, available as online supplementary material). Cox proportional hazards models were fitted on eGFR linear splines (knots at 30, 45, 60, 75, 90, and 105 mL/min/1.73 m^2), log-transformed ACR splines (knots at 10, 30, and 300 mg/g for general population cohorts; knots at 30, 300, and 1,000 mg/g for CKD cohorts), age, sex, race, body mass index, smoking, diabetes, systolic blood pressure, history of cardiovascular disease, and total cholesterol level. Due to small sample size in the analyses by race, the upper and lower knots in eGFR were omitted for these models. The overall relationship between eGFR and AKI was then determined, calculating hazard ratios (HRs) at each 1–mL/min/1.73 m^2 increment. Next, interactions between eGFR and each risk factor (age, sex, or race) were determined by including the eGFR–risk factor product term in the Cox model. For cohorts with ACR, a similar method was used to estimate risk associated with ACR and the interactions between ACR and each risk factor. For analyses of general-population cohorts, a reference eGFR of 80 mL/min/1.73 m^2 and ACR of 5 mg/g were used, as described previously.[26] For analyses of CKD cohorts, reference eGFR of 50 mL/min/1.73 m^2 and ACR of 50 mg/g were used. Heterogeneity of effects was investigated using the I^2 statistic.

At the second stage, estimates from each cohort were pooled using a random-effects model, with each study receiving a weight corresponding to the inverse of the variance of each spline coefficient. Pointwise interaction was estimated as the ratio of HRs in each age, sex, or race category compared with the reference category (age 55-64 years, male sex, and white race, respectively) at each 1–mL/min/1.73 m^2 increment of eGFR or 8% increment in ACR. The adjusted incidence rates at eGFR of 80 mL/min/1.73 m^2 and ACR of 5 mg/g were estimated as the weighted-average study-specific incidence rates for the reference category of each risk factor (age 55-64 years, male sex, and white race) as previously described.[26] This value was treated as a fixed reference point, and the adjusted incidence rate at each increment of eGFR and ACR was estimated as the product of the fixed reference and the meta-analyzed HRs. Finally, pooled HRs in 7 categories of eGFR (15-29, 30-44, 45-59, 60-74, 75-89, 90-104, and ≥105 mL/min/1.73 m^2) and 4 categories of ACR (<10, 10-29, 30-299, and ≥300 mg/g) were compared across age, race, and sex categories to assess overall interactions. Multiplicative interactions with $P < 0.05$ were considered significant. All analyses were performed using Stata, version 13.1 MP (StataCorp LP).

RESULTS

Baseline Characteristics

Thirteen cohorts from 8 different countries comprising 1,364,568 participants met eligibility criteria