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Original Investigation

CKD and Risk for Hospitalization With Infection: The Atherosclerosis Risk in Communities (ARIC) Study

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Background: Individuals on dialysis therapy have a high risk for infection, but risk for infection in earlier stages of chronic kidney disease has not been comprehensively described.

Study Design: Observational cohort study.

Setting & Participants: 9,697 participants (aged 53-75 years) in the Atherosclerosis Risk in Communities (ARIC) Study. Participants were followed up from 1996 to 1998 through 2011.

Predictors: Estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (ACR).

Outcomes: Risk for hospitalization with infection and death during or within 30 days of hospitalization with infection.

Results: During follow-up (median, 13.6 years), there were 2,701 incident hospitalizations with infection (incidence rate, 23.6/1,000 person-years) and 523 infection-related deaths. In multivariable analysis, HRs of incident hospitalization with infection as compared to eGFRs $\geq$ 90 mL/min/1.73 m^2 were 2.55 (95% CI, 1.43-4.55), 1.48 (95% CI, 1.28-1.71), and 1.07 (95% CI, 0.98-1.16) for eGFRs of 15 to 29, 30 to 59, and 60 to 89 mL/min/1.73 m^2, respectively. Corresponding HRs were 3.76 (95% CI, 1.48-9.58), 1.62 (95% CI, 1.20-2.19), and 0.99 (95% CI, 0.80-1.21) for infection-related death. Compared to ACRs $<$ 10 mg/g, HRs of incident hospitalization with infection were 2.30 (95% CI, 1.81-2.91), 1.56 (95% CI, 1.36-1.78), and 1.34 (95% CI, 1.20-1.50) for ACRs $\geq$ 300, 30 to 299, and 10 to 29 mg/g, respectively. Corresponding HRs were 3.44 (95% CI, 2.28-5.19), 1.57 (95% CI, 1.18-2.09), and 1.39 (95% CI, 1.09-1.78) for infection-related death. Results were consistent when separately assessing risk for pneumonia, kidney and urinary tract infections, bloodstream infections, and cellulitis and when taking into account recurrent episodes of infection.

Limitations: Outcome ascertainment relied on diagnostic codes at time of discharge.

Conclusions: Increasing provider awareness of chronic kidney disease as a risk factor for infection is needed to reduce infection-related morbidity and mortality.

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INDEX WORDS: Chronic kidney disease (CKD); chronic renal insufficiency; chronic kidney failure; glomerular filtration rate (GFR); albuminuria; proteinuria; infection; infectious disease; pneumonia; respiratory tract infections; urinary tract infections; bacteremia; cellulitis; hospitalization; kidney function.

Chronic kidney disease (CKD) is a rapidly growing public health problem. More than 20 million adults in the United States are estimated to have some level of CKD, defined as either reduced estimated glomerular filtration rate (eGFR) or elevated urinary albumin-creatinine ratio (ACR).[1] Numerous studies have shown that reduced eGFR and albuminuria increase the risk for cardiovascular disease independent of one another,[2] but they are also known to increase the risk for noncardiovascular outcomes such as acute kidney injury[3] and fracture.[4]

Infection may be another important complication of CKD. Individuals on dialysis therapy have a remarkably high risk for infection,[5] particularly for bloodstream infections, foot infections, and pneumonia.[6,7] Increased risk for hospitalization with infection has also been observed among individuals with less severely decreased kidney function that does not require dialysis,[8-10] although results vary across

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types of infection. Of importance, data for the other key element of defining and staging CKD, albuminuria are sparse in this context. Two studies demonstrated that albuminuria is associated with risk for overall infection-related and pneumonia-related hospitalizations, but these studies exclusively investigated diabetic patients.[11,12] In the general population, one study simultaneously explored the infection risk of both eGFR and albuminuria, but that study investigated only mortality related to infection.[13]

Understanding the contributions of eGFR and albuminuria to infection risk will provide insights about identifying patients with CKD who are at particularly high risk for infectious disease and may benefit from preventive approaches (eg, vaccination). Thus, we evaluated the association of eGFR and albuminuria with risk for hospitalization with infection and subsequent mortality in a biethnic community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study. We also evaluated specific types of infections, including pneumonia, kidney and urinary tract infection, bloodstream infections, and cellulitis, separately, and the rate of recurrent hospitalizations.

METHODS

Study Population

The ARIC Study is a community-based prospective cohort study with 15,792 participants aged 45 to 64 years and enrolled in 1987 to 1989 (visit 1) from 4 US communities (Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD). Short-term follow-up visits were conducted in 1990 to 1992 (visit 2), 1993 to 1995 (visit 3), and 1996 to 1998 (visit 4). Further details of the ARIC Study were described elsewhere.[14] We set visit 4 as baseline because eGFR and albuminuria were simultaneously assessed for the first time in the ARIC Study at this visit. Of 11,656 individuals who attended visit 4, we excluded individuals with a prior hospitalization with infection (as defined later; n = 1,023), missing either serum creatinine or cystatin C levels (n = 323), missing albuminuria (n = 117), who declined informed consent for noncardiovascular research (n = 39), with ethnicities other than white or African American (n = 31), with end-stage renal disease (ESRD) or eGFR < 15 mL/min/1.73 m^2 (n = 20), and missing covariates (n = 406), leaving 9,697 participants for analysis (Fig S1, available as online supplementary material). Written informed consent was obtained from all participants, and the institutional review board at each study site approved the study (#H.34.99.07.02.A1 at Johns Hopkins University).

Exposures of Interest

Primary exposures of interest were eGFR and ACR. eGFR was based on the CKD-EPI (CKD Epidemiology Collaboration) serum creatinine and cystatin C equation.[15] Serum creatinine was measured using a modified kinetic Jaffé method, calibrated to the Cleveland Clinic laboratory measurements,[16] then standardized to an isotope-dilution mass spectrometry−traceable method.[17] Serum cystatin C was measured using an enhanced immunonephelometric assay (Siemens Healthcare Diagnostics). Urine albumin and creatinine were measured by nephelometry and the Jaffé method, respectively. The detection threshold was <2 mg/dL for urine albumin excretion and <1 mg/dL for urine creatinine excretion. Participants with urine albumin excretion < 2 mg/dL were assumed to have 1 mg/dL for the purpose of calculating ACR (4,364 participants). There were no participants with urine creatinine excretion < 1 mg/dL.

Outcomes of Interest

The primary outcome of interest was first incident hospitalization with infection. Hospital discharge records with the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes have been captured through active surveillance for all ARIC Study participants. Definitions of infection-related *ICD-9-CM* codes were based on the analytical methods used in the US Renal Data System (USRDS),[18] including any pathogen-, organ-, or symptom-based diagnoses (Table S1). In addition, the a priori–determined 4 most common types of infection[19] were separately analyzed, including pneumonia (*ICD-9-CM* codes 480-486), kidney and urinary tract infections (590, 590.0-590.4, 597, 598, 599.0, 601, 604, 607, and 608), bloodstream infections (038 and 790.7), and cellulitis (681 and 682). Secondary outcomes were all hospitalizations with infection, including recurrent cases, as well as subsequent death during or within 30 days after discharge from hospitalization with infection, similar to previous studies.[20,21] Participants who did not develop the primary outcome were censored when they died, lost to follow-up, or administratively censored on December 31, 2011.

Other Covariates of Interest

All covariates were assessed at baseline (visit 4, 1996-1998) except for years of education, which was assessed at visit 1 (1987-1989). Age, sex, race, smoking status, alcohol consumption, and years of education were based on self-reported questionnaires. Information about the use of antineoplastic agents and steroids or immunosuppressive agents was obtained from medication records at visit 4. Hypertension was defined as using an antihypertensive drug, systolic blood pressure $\geq$ 140 mm Hg, or diastolic blood pressure $\geq$ 90 mm Hg. Diabetes was defined as self-reported physician diagnosis of diabetes, using an antidiabetic drug, fasting glucose level $\geq$ 126 mg/dL, or casual glucose level $\geq$ 200 mg/dL. *ICD-9-CM* codes indicating history of cancer (140-165, 170-176, 179-209, and 235-239) and chronic obstructive pulmonary disease (490-491, 492, 494, and 496) were retrieved from hospital discharge records between visit 1 and visit 4. History of cardiovascular disease, including heart failure, coronary heart disease, and stroke, was determined if there was a self-reported history at visit 1 or clinical event between visit 1 and visit 4. Data for incident ESRD were obtained by the linkage to USRDS.

Statistical Analysis

Baseline characteristics were compared across eGFR and ACR categories using *t* tests, analysis of variance tests, and χ^2 tests. Crude incidence rate and its 95% confidence interval (CI) was estimated using Poisson regression models. Hazard ratios (HRs) were assessed using Cox proportional hazards models across 4 categories of eGFR ($\geq$90 [reference], 60-89, 30-59, and 15-29 mL/min/1.73 m^2) and ACR ($<$10 [reference], 10-29, 30-299, and $\geq$300 mg/g). Models were adjusted for age, sex, race, body mass index, smoking status, alcohol consumption, education level, use of antineoplastic agents and steroids, hypertension, diabetes, history of cancer and chronic obstructive pulmonary disease, prior heart failure, prior coronary disease, and prior stroke, and ACR, for the analysis of eGFR, and eGFR, for the analysis of ACR. Interaction between eGFR and ACR categories was assessed by contrasting models with and without their production terms using the log-likelihood test.