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Combined Association of Albuminuria and Cystatin C–Based Estimated GFR With Mortality, Coronary Heart Disease, and Heart Failure Outcomes: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—Serum cystatin C level has been shown to have a stronger association with clinical outcomes than serum creatinine level. However, little is known about the combined association of cystatin C–based estimated glomerular filtration rate (eGFR_{cys}) and albuminuria with clinical outcomes, particularly at levels lower than current chronic kidney disease (CKD) cutoffs.

Study Design—Prospective cohort.

Setting & Participants—10,403 ARIC (Atherosclerosis Risk in Communities) Study participants followed up for a median of 10.2 years.

Predictor—eGFR_{cys}, albuminuria.

Outcomes—Mortality, coronary heart disease (CHD), and heart failure, as well as a composite of any of these separate outcomes.

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Results—Both decreased eGFR_{cys} and albuminuria were associated independently with the composite outcome, as well as mortality, CHD, and heart failure. Although eGFR_{cys} of 75-89 mL/min/1.73 m² in the absence of albuminuria (albumin-creatinine ratio [ACR] <10 mg/g) or albuminuria with ACR of 10-29 mg/g with normal eGFR_{cys} (90-104 mL/min/1.73 m²) was not associated significantly with any outcome compared with eGFR_{cys} of 90-104 mL/min/1.73 m² and ACR <10 mg/g, the risk of each outcome was significantly higher in those with both eGFR_{cys} of 75-89 mL/min/1.73 m² and ACR of 10-29 mg/g (for mortality, HR of 1.4 [95% CI, 1.1-2.0]; for CHD, HR of 1.9 [95% CI, 1.4-2.6]; for heart failure, HR of 1.8 [95% CI, 1.2-2.7]). Combining the 2 markers improved risk classification for all outcomes ($P < 0.001$), even in those without overt CKD.

Limitations—Only one measurement of cystatin C.

Conclusions—Mildly decreased eGFR_{cys} and mild albuminuria independently contributed to the risk of mortality, CHD, and heart failure. Even minimally decreased eGFR_{cys} (75-89 mL/min/1.73 m²) is associated with increased risk in the presence of mild albuminuria. Combining the 2 markers is useful for improved risk stratification even in those without clinical CKD.

Index words

Epidemiology; kidney; outcomes

Chronic kidney disease (CKD) is a major public health problem with an estimated prevalence of 11% in the United States.^{1,2} Extensive evidence suggests a strong positive association between kidney damage manifested by albuminuria and decreased estimated glomerular filtration rate (eGFR) with mortality and cardiovascular disease (CVD), as well as other poor out-comes.³⁻⁵ Creatinine is the most widely used measure of kidney function in both clinical practice and epidemiologic research. However, creatinine-based eGFR (eGFR_{cr}) is biased by several non-GFR determinants, including muscle mass. Studies that have estimated GFR with serum creatinine level have observed a U-shaped association between eGFR_{cr} and mortality, in which higher risk is found with low ($\text{eGFR}_{\text{cr}} < 60$ mL/min/1.73 m²) or high eGFR_{cr} (> 105 mL/min/1.73 m²).^{3,6} This U-shaped association has been thought to be due to a higher risk of death for individuals with decreased muscle mass and consequently lower creatinine production and overestimated eGFR_{cr} .

Cystatin C, an alternative marker of kidney function with correlation to measured GFR similar to creatinine, is less susceptible to these issues. Data suggest a stronger and more linear association between serum cystatin C concentrations and risk of mortality and CVD compared with creatinine.⁶⁻¹²

Elevated albuminuria, a sensitive marker of kidney damage, has an overall prevalence of 7.8% in the United States and increases to 30% in those with physician-diagnosed diabetes.¹³ Several studies have suggested that micro- or macroalbuminuria is a strong independent predictor of CVD and mortality. Data also show that albuminuria at levels lower than the current clinical cutoffs for microalbuminuria is associated with greater risk, suggesting that any degree of albuminuria is harmful.^{3,4,14,15}

Because both albuminuria and decreased eGFR are associated independently with mortality, coronary heart disease (CHD), and heart failure and the 2 pathologic states may exist separately or together, there is a movement to use both measures for CKD staging and risk prediction.¹⁶ A recent large prospective study using a triple-marker approach to predict future risk of mortality and end-stage renal disease found that adding cystatin C to the combination of eGFR_{cr} and albuminuria significantly improves risk prediction.¹⁷ However, limited data exist for the combined association of cystatin C-based eGFR (eGFR_{cys}) and

albuminuria with cardiovascular outcomes in the general population. Also, there is a need to investigate the combined association of these markers in eGFR and albuminuria categories that are lower than the current CKD cutoffs (ie, eGFR of 60-90 mL/min/1.73 m² and albumin-creatinine ratio [ACR] <30 mg/g).

The aim of our study is to prospectively investigate the combined association of eGFR_{cys} and albuminuria with the risk of all-cause mortality, CHD, and heart failure in the general population. We also investigate the combined association of these markers with outcomes at eGFR and albuminuria levels lower than the current clinical cutoffs for defining CKD.

Methods

Study Population

Our source population included participants from the Atherosclerosis Risk in Communities (ARIC)¹⁸ Study, a population-based cohort study of middle-aged individuals from 4 US communities: Washington County, MD; Jackson, MS; Forsyth County, NC; and Minneapolis, MN. In the ARIC cohort, 15,792 men and women were enrolled in 1987-1989 when they were 45-64 years of age and underwent 4 standardized examinations approximately every 3 years. Details of the ARIC cohort are described elsewhere.¹⁹ In the present study, we included participants who attended visit 4 (1996-1998) and had urinary ACR and cystatin C measured. Of 11,656 participants who attended visit 4, we excluded participants with race other than white or black (n = 48) and those with missing data for any of the key variables (ie, age, race, sex, history of hypertension, diabetes, smoking, CHD or heart failure, body mass index, cholesterol, serum cystatin C, and C-reactive protein). Our final study population included 10,403 participants. Median follow-up was 10.2 years.

Data Collection

Detailed medical history and information for demographic and other behavioral characteristics were collected at each visit by trained interviewers.²⁰ This included information for smoking (current or ever smoker) that was based on self-reports. Body mass index was calculated as weight in kilograms divided by square of height in meters. Blood samples were collected according to standardized procedures.¹⁸ Diabetes mellitus was defined as fasting glucose concentration ≥126 mg/dL, nonfasting glucose concentration ≥200 mg/dL, self-reported physician diagnosis of diabetes, or use of oral hypoglycemic medications or insulin. Plasma cholesterol, triglyceride, and high-density lipoprotein cholesterol levels were determined using enzymatic methods, and low-density lipoprotein cholesterol level was calculated using the Friedewald equation. Hypertension was used as a categorical variable and defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of blood pressure-lowering medications.

Exposure Assessment

Cystatin C was measured using the Siemens Healthcare Diagnostics BN II System (www.medical.siemens.com) by a particle-enhanced immunonephelometric assay at Cleveland Clinic in 2008 from frozen stored samples collected at visit 4. The reliability coefficient for 421 blinded replicates was 0.65 (0.94 after removing 10 pairs of outliers) and the coefficient of variation was 6.6%. eGFR_{cys} was calculated using the CKD-EPI (CKD Epidemiology Collaboration) cystatin C equation: $eGFR_{cys} = [127.7 \times CysC^{-1.17} \times age^{-0.13} \times (0.91 \text{ if female}) \times (1.06 \text{ if black})]$.²¹ The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) working group for the standardization of cystatin C and the Institute for Reference Materials and Measurements recently made available a certified material (the ERM-DA471/IFCC) that was used to re-express the previously reported eGFR_{cys} equations. The newly re-expressed CKD-EPI cystatin C equation was traceable to

the IFCC standards.²² Participants were categorized into 7 eGFR_{cys} categories: 105, 90-104, 75-89, 60-74, 45-59, 30-44, and 15-29 mL/min/1.73 m². Participants with eGFR_{cys} <15 mL/min/1.73 m² were excluded due to only 9 participants in that category.

A spot urine sample was collected and aliquots were frozen and stored at -70°C. Urinary albumin was measured by a nephelometric method on either the Dade Behring BN 100 (Dade Behring Inc, www.dadebehring.com) or the Beckman Nephelometer (Beckman Coulter Inc, www.beckmancoulter.com), whereas creatinine was measured using the Jaffé method and ACR was calculated. Both analytes were measured at the University of Minnesota Physician Outreach Laboratories. Participants were categorized into 4 categories based on ACR level: <10, 10-29, 30-299, and ≥300 mg/g. Combined with eGFR_{cys}, we provide data for outcomes in 28 categories of eGFR_{cys} and albuminuria.

Outcome Assessment

Participants were followed up from ARIC visit 4 until December 31, 2007, for all-cause mortality, incident CHD, and incident heart failure. Continuous comprehensive surveillance was conducted for all CVD-related hospitalizations and mortality. Published criteria were used to adjudicate all potential CHD events.²⁰ Incident CHD event was defined as a hospitalized definite or probable myocardial infarction, fatal CHD (CHD death), or coronary revascularization procedure. Participants with any history of CHD (either by self-report or based on continuous comprehensive surveillance prior to visit 4) were excluded from analysis of incident CHD. For cardiac revascularization procedures, *International Classification of Diseases* codes 36.0, 36.1, and 36.2 were used.

Death information was obtained from the National Death Index and annual telephone follow-up. Incident heart failure was based on *International Classification of Diseases* diagnostic codes (428.0-428.9 and I50).

Statistical Analysis

We used eGFR_{cys} of 90-104 mL/min/1.73 m² as the reference category for eGFR_{cys} and ACR <10 mg/g as the reference category for ACR. We looked at each eGFR_{cys} category within each ACR category and vice versa. We used *t* test and analysis of variance for continuous variables, whereas χ^2 was used for categorical variables. Cox proportional hazard models were used to estimate hazard ratios (HRs) for mortality, CHD, and heart failure, as well as for the composite outcome (composite of mortality, CHD, and heart failure). We first adjusted for age, race, and sex, then added total cholesterol level, diabetes, prevalent CHD, current smoking, hypertension, high-sensitivity C-reactive protein level, and body mass index. Follow-up time was calculated using date of visit 4 as the baseline time with end of follow-up being a death event, incident CHD event, incident heart failure, loss to follow-up, or the end of the follow-up period. Interaction between eGFR_{cys} and ACR was assessed using ACR as both a continuous and a categorical variable, using likelihood ratio test to compare models. ACR was log transformed because of its skewed distribution. We also assessed interactions between eGFR_{cys} and race.

Predicted probabilities for an event for each individual were determined with eGFR_{cys} plus all other predictors in the model except ACR (model I). Similarly predicted probabilities were determined with ACR plus all other predictors in the model except eGFR_{cys} (model II). We then added ACR to model I and predicted probabilities were redetermined, and similarly, eGFR_{cys} was added to model II and predicted probabilities were redetermined. Continuous net reclassification improvement (NRI) was calculated for each outcome by assessing the net improvement in risk classification with the addition of either ACR or eGFR_{cys} to the model and was defined as: [(sum of those with an increase in predicted

probability of an event among those with an event) – (sum of those with a decrease in predicted probability of an event among those with an event)] + [(sum of those with a decrease in predicted probability of an event among those without an event) – (sum of those with an increase in predicted probability of an event among those without an event)].²³ We also provided model discrimination (Harrell's C statistic) for each outcome from the fully adjusted model.

$P < 0.05$ was considered statistically significant. All statistical analyses were done using Stata, version 11 (StataCorp, www.stata.com).

Results

Baseline Characteristics

Mean age of the study population was 63 years, with 56% women and 22% African Americans (Table 1). Participants with $\text{eGFR}_{\text{cys}} < 75 \text{ mL/min/1.73 m}^2$ were older than participants in the higher baseline eGFR_{cys} categories, and those with eGFR_{cys} of 30-59 mL/min/1.73 m² had the oldest mean age. Median ACR, mean cystatin C, and mean creatinine values were higher in the lower baseline eGFR_{cys} categories, as expected. The prevalence of chronic comorbid conditions such as diabetes, hypertension, and CHD, as well as smoking prevalence, was higher in those with lower baseline eGFR_{cys} or higher albuminuria compared with those in the higher eGFR_{cys} categories or lower albuminuria. Only 1.7% ($n = 170$) of all participants had macroalbuminuria, whereas 7.9% ($n = 823$) had at least microalbuminuria. Median ACR was higher in African Americans than whites in the eGFR_{cys} categories $< 60 \text{ mL/min/1.73 m}^2$ (4.8 vs 6.1, 9.1 vs 94.4, 5.5 vs 56.8, and 830.0 vs 1,666.2 mg/g for eGFR_{cys} categories of 45-60, 30-44, 15-29, and $< 15 \text{ mL/min/1.73 m}^2$, respectively). We also observed a slightly higher median ACR for $\text{eGFR}_{\text{cys}} \geq 105 \text{ mL/min/1.73 m}^2$ than eGFR_{cys} of 90-104 mL/min/1.73 m². Diabetes was more prevalent in those with $\text{eGFR}_{\text{cys}} \geq 105 \text{ mL/min/1.73 m}^2$ than in those with eGFR_{cys} of 90-104 mL/min/1.73 m².

Table 2 lists the numbers and proportions of participants in each eGFR_{cys} and albuminuria category. Only 6.5% of participants with $\text{eGFR}_{\text{cys}} > 60 \text{ mL/min/1.73 m}^2$ had ACR $\geq 30 \text{ mg/g}$, whereas 79.3% of those with moderately or severely decreased eGFR had ACR $< 30 \text{ mg/g}$.

Crude Incidence Rates

A total of 1,441 (14%) deaths, 1,016 (9.8%) CHD events, and 865 (8.3%) heart failure events occurred during a median follow-up of 10.2 (mean, 9.8) years. Incidence rates for all events were higher in those in the lower baseline eGFR_{cys} categories or those with higher ACR. Incidence rates for all-cause mortality ranged from 8.7 deaths/1,000 person-years in the reference category to 27.4 deaths/1,000 person-years in those with eGFR_{cys} of 15-29 mL/min/1.73 m² and ACR $< 10 \text{ mg/g}$. In the presence of macroalbuminuria and eGFR_{cys} of 15-29 mL/min/1.73 m², incidence rates were as high as 102 deaths/1,000 person-years. For individuals with mildly decreased baseline eGFR_{cys} (60-89 mL/min/1.73 m²) without microalbuminuria, incidence rates ranged from 10-25 deaths/1,000 person-years depending on the degree of associated albuminuria. Substantially higher incidence rates were observed across albuminuria categories within the same eGFR_{cys} category. For example, in the eGFR_{cys} category of 60-74 mL/min/1.73 m², the incidence rate was nearly twice as high for those with ACR of 10-29 mg/g (25.2 deaths/1,000 person-years) compared with those with ACR $< 10 \text{ mg/g}$ (12.5 deaths/1,000 person-years). A total of 56% of participants with $\text{eGFR}_{\text{cys}} < 60 \text{ mL/min/1.73 m}^2$ and ACR $> 30 \text{ mg/g}$ died compared with 11% of other participants. Findings were similar for CHD and heart failure, with higher incidence rates in those with lower eGFR_{cys} and/or higher ACR.

Outcomes

Composite Outcome and All-Cause Mortality—Risks of the composite outcome and all-cause mortality were higher even with minimally decreased $eGFR_{cys}$, as well as with minimal albuminuria. In the $eGFR_{cys}$ category of 60-74 mL/min/1.73 m², HRs were 1.3 (95% confidence interval [CI], 1.1-1.5) and 1.2 (95% CI, 0.9-1.4) for those with no albuminuria versus 1.8 (95% CI, 1.5-2.3) and 2.0 (95% CI, 1.5-2.7) for those with ACR of 10-29 mg/g for the composite outcome and all-cause mortality, respectively. Similarly, in the ACR category of 10-29 mg/g, HRs were 1.6 (95% CI, 1.3-2.0) and 1.5 (95% CI, 1.1-2.0) in those with $eGFR_{cys}$ of 75-89 and 1.8 (95% CI, 1.5-2.3) and 2.0 (95% CI, 1.5-2.7) in those with $eGFR_{cys}$ of 60-74 mL/min/1.73 m² for the composite outcome and all-cause mortality, respectively. The HR for mortality was more than 2-fold higher (HR, 2.2; 95% CI, 1.5-3.2) for those with $eGFR_{cys}$ of 45-59 mL/min/1.73 m² in the absence of microalbuminuria and about 3-fold higher (HR, 3.3; 95% CI, 1.3-8.2) in the normal $eGFR_{cys}$ category in the presence of macroalbuminuria. Overall, compared with the reference, there was a 30% ($P=0.006$) higher hazard of mortality when $eGFR_{cys}$ was 60-74 mL/min/1.73 m² and a 40% ($P<0.01$) higher hazard when ACR was 10-29 mg/g. We also noted a slightly lower risk of mortality when $eGFR_{cys}$ was 105 mL/min/1.73 m² compared with the reference category, although it did not achieve statistical significance (Tables 3 and 4). Model discrimination (Harrell's C statistic) from the fully adjusted model for the combined association of $eGFR_{cys}$ and albuminuria was 0.75 for all-cause mortality.

Associations of $eGFR_{cys}$ (stratified by albuminuria) with both the composite outcome and mortality were stronger and more linear compared with that observed with $eGFR_{cr}$ (Fig 1A and B).

Coronary Heart Disease and Heart Failure—In the fully adjusted model, we observed a significantly higher relative hazard in those with minimally decreased baseline $eGFR_{cys}$ or with mild baseline albuminuria lower than the current CKD cutoffs compared with the reference. Participants with $eGFR_{cys}$ of 75-89 mL/min/1.73 m² and ACR of 10-29 mg/g were almost twice as likely to have a CHD event (HR, 1.9; 95% CI, 1.4-2.6) than those in the reference category. The relative hazard was more than 4-fold higher in those with $eGFR_{cys}$ of 15-29 mL/min/1.73 m² in the presence of macroalbuminuria compared with the reference category. Overall, we observed a 40% higher hazard of CHD for $eGFR_{cys}$ of 60-74 mL/min/1.73 m² ($P=0.001$) and a 22% higher hazard of CHD for ACR of 10-29 mg/g ($P=0.03$), not adjusted for ACR and $eGFR_{cys}$, respectively, compared with the reference (Table 5).

The findings generally were similar for heart failure, with a greater risk of heart failure in those with mildly decreased $eGFR_{cys}$ ($eGFR_{cys}$ of 60-89 mL/min/1.73 m²) and mild albuminuria (lower than the current microalbuminuria cutoffs). HRs ranged from 5.6 in those with $eGFR_{cys}$ of 45-59 mL/min/1.73 m² and ACR of 30-299 mg/g to as high as 14.0 in those with $eGFR_{cys}$ of 30-44 mL/min/1.73 m² and ACR ≥ 300 mg/g (Table 6). Model discrimination (Harrell's C statistic) was 0.72 and 0.79 for CHD and heart failure, respectively.

For both CHD and heart failure, the association was noted to be stronger with $eGFR_{cys}$ compared with $eGFR_{cr}$ (Fig 1C and D).

There were no significant interactions between either $eGFR_{cys}$ and ACR or $eGFR_{cys}$ and race for any outcome.

Risk Prediction

Adding ACR to the fully adjusted model with $eGFR_{cys}$ significantly improved risk prediction for all-cause mortality, CHD, and heart failure (for mortality, $NRI = 25\%$; $P < 0.001$; for CHD, $NRI = 13\%$; $P < 0.001$; for heart failure, $NRI = 18\%$; $P < 0.001$). Similarly, adding $eGFR_{cys}$ to the model with ACR plus all other predictors significantly improved risk prediction (for mortality, $NRI = 7\%$; $P = 0.006$; for CHD, $NRI = 13\%$; $P < 0.001$; for heart failure, $NRI = 18\%$; $P < 0.001$). Combining the 2 markers significantly improved risk prediction for all outcomes, even in those with $eGFR_{cys} > 60$ mL/min/1.73 m² and ACR < 30 mg/g.

Discussion

Our findings suggest that any degree of decreased $eGFR_{cys}$ or any degree of albuminuria is associated with increased risk of all-cause mortality, incident CHD, and incident heart failure hospitalization. Our findings remained significant after adjustment for multiple potential confounders. The most striking finding was a significantly increased risk of all 3 outcomes associated with even mildly abnormal levels of ACR and $eGFR_{cys}$, even in those with ACR lower than the current microalbuminuria cutoff and $eGFR_{cys} > 60$ mL/min/1.73 m². Combining the 2 markers significantly improved risk prediction for all 3 outcomes in those with ACR < 30 mg/g and $eGFR_{cys} > 60$ mL/min/1.73 m². We also observed weaker associations for CHD than for mortality and heart failure.

Our findings are consistent with the existing evidence that cystatin C level is a very strong predictor of mortality and CVD.^{7,10} Also, the presence of any degree of albuminuria is associated independently with poor outcomes, and risk is higher with higher albuminuria.^{4,14,15} Several studies have suggested that cystatin C level has a stronger and more linear association with outcomes than creatinine level.^{6,24,25} A cohort study of approximately 12,000 participants found that those with CKD by $eGFR_{cys}$ had a 3.2-fold higher risk of death than those without CKD. However, the HR for CKD defined by $eGFR_{cr}$ was 0.80 (95% CI, 0.50-1.26) and for CKD defined by both $eGFR_{cys}$ and $eGFR_{cr}$ was 1.93 (95% CI, 1.27-2.92). Similar results were observed for CVD events, heart failure, and end-stage renal disease.²⁶ These findings strengthen the existing evidence that cystatin C level is a better predictor of mortality, CVD, and other poor outcomes than is creatinine level in patients with or without clinical CKD.

Another study investigated the combined association of $eGFR_{cr}$, cystatin C level, and albuminuria and the risk of mortality and CVD in about 3,300 older adults with a median follow-up of 8.3 years. The authors divided the cohort into 6 categories: no CKD, preclinical CKD, and clinical CKD with or without the presence of microalbuminuria and observed a 50% increased risk of mortality in those with preclinical CKD or those with the presence of microalbuminuria. The risk increased to 2.4 fold in those with both preclinical CKD and microalbuminuria and 4-fold in those with clinical CKD in the presence of microalbuminuria.²⁷ However, GFR was estimated using creatinine instead of cystatin C level, and the authors used serum cystatin C levels as an exposure instead of $eGFR_{cys}$. The mean age of the cohort was 78 years and thus the study findings may not be generalizable to other ages. Moreover, the authors studied the association in only 6 categories of combined $eGFR_{cys}$ and albuminuria. Our study is unique in that this is, as far as we are aware, the first large population-based cohort study that has investigated the combined association of $eGFR_{cys}$ and albuminuria with risk of poor outcomes during a long follow-up in the general population. To our knowledge, ours is the first large study to use standardized (to ERM-DA471/IFCC) and calibrated cystatin C level. We also categorized $eGFR_{cys}$ and albuminuria and studied the association in 28 different combined $eGFR_{cys}$ and albuminuria

categories; 8 of the 28 categories did not have clinical CKD at baseline. It is important to note that in these 8 categories, risk increased significantly when both markers were mildly abnormal (however, still lower than the current CKD cutoffs).

In our study, we also observed increased risk of heart failure with high-normal $eGFR_{cys}$. A U-shaped association of creatinine level with outcomes typically is ascribed to the association of lower serum creatinine level with low muscle mass and frailty. However, a similar association of $eGFR_{cys}$ with heart failure is unlikely to be related to muscle mass. We can only hypothesize potential mechanisms that may include either subclinical heart failure being associated with decreased cystatin C level or hyperfiltration associated with the higher prevalence of diabetes and hypertension resulting in increased heart failure risk. However, the exact mechanism is unclear and may need to be explored further.

Our study has some limitations as well. First, we had only a single measurement of both cystatin C and ACR. Although this single measurement likely will be subject to measurement error, there is no reason to suspect that these errors will be differential and therefore likely would lead to attenuation of the true associations. Second, because urinary creatinine is affected by muscle mass, it is possible that very sick patients with muscle wasting would have falsely elevated ACRs and thus may result in false association of ACR with mortality. Any such misclassification would have less impact on other outcomes, such as CHD and heart failure, but our study findings were consistent for all 3 outcomes. We also acknowledge that our study had a relatively small proportion of individuals with advanced CKD.

In conclusion, our study suggests an increased risk of mortality, CHD, and heart failure independently with both $eGFR_{cys}$ and albuminuria. The risk is greater in those with lower $eGFR_{cys}$ or higher albuminuria and also is significantly higher even in individuals below current CKD cutoffs but with mildly decreased baseline $eGFR_{cys}$ or mild albuminuria. Combining the 2 markers significantly improves risk classification. This study adds to the literature that cystatin C is a better marker than creatinine for risk-classifying individuals with CKD and definitely has a place to be used in clinical practice. Although it can be used as a first-line marker in combination with ACR instead of creatinine level, this would involve testing a large number of individuals, which may not be cost-effective at this time. However, for a carefully selected group of patients for whom finer risk stratification is needed, it may be time to introduce cystatin C into clinical practice to be used in combination with traditional CKD markers.

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Figure 1. Hazard ratios with 95% confidence intervals of estimated glomerular filtration rate (eGFR) with the composite outcome (top row of panels), all-cause mortality (second row), coronary heart disease (third row), and heart failure (bottom row). Graphs include the interaction between eGFR and log-ACR (albumin-creatinine ratio). eGFR knots at 45, 60, 75, 90, and 105 mL/min/1.73 m². Reference group is eGFR of 95 mL/min/1.73 m² and ACR of 5 mg/g.

Table 1

Baseline Characteristics Stratified by eGFR_{cys} and ACR

	eGFR _{cys} (mL/min/1.73 m ²)										ACR (mg/g)		
	105	90-104	75-89	60-74	45-59	30-44	15-29	P-trend	<10	10-29	30-299	300	P-trend
No.	885	2,200	3,730	2,532	764	157	135	NA	8,356	1,224	653	170	NA
Age (y)	59.3 ± 4.6	61 ± 5.2	62.6 ± 5.5	64.3 ± 5.5	66.2 ± 5.3	66.1 ± 5.4	63.8 ± 5.9	<0.001	62.4 ± 5.6	63.8 ± 5.8	64.1 ± 5.8	64.6 ± 6.1	<0.001
White (%)	42.6	69.6	83.6	87.3	86.3	80.3	88.9	<0.001	79.2	82.0	63.7	59.4	<0.001
Female (%)	53.7	50.8	53.9	62.1	62.4	60.5	56.3	<0.001	55.5	61.5	53.0	52.4	0.8
Current smokers (%)	12.4	11.9	14.5	17.4	18.1	18.6	23.7	<0.001	14.0	16.7	22.5	17.1	<0.001
BMI (kg/m ²)	27.8 ± 4.8	27.7 ± 4.9	28.5 ± 5.4	29.5 ± 5.7	30.3 ± 6.3	30.4 ± 6.7	29.0 ± 5.8	<0.001	28.6 ± 5.4	28.5 ± 5.7	29.3 ± 6.2	30.6 ± 6.2	<0.001
Diabetes (%)	26.4	14.4	13.3	14.4	20.1	33.8	23.0	0.9	12.5	21.3	37.0	61.0	<0.001
Hypertension (%)	46.0	40.0	42.5	49.0	64.7	73.3	54.1	<0.001	41.2	59.3	73.1	89.4	<0.001
Prevalent CHD (%)	1.5	1.7	1.8	2.8	3.7	1.9	3.0	<0.001	1.8	2.4	4.5	7.7	<0.001
Total cholesterol (mg/dL)	198.7 ± 35.9	200.7 ± 34.9	201.3 ± 36.8	202.7 ± 37.1	199.3 ± 42.9	206.6 ± 41.2	197.5 ± 39.4	0.1	201.1 ± 36.1	201.3 ± 38.0	198.7 ± 40.0	213.3 ± 55.4	0.2
LDL cholesterol (mg/dL)	119.6 ± 34.1	122.3 ± 32.6	123.3 ± 33.4	124.5 ± 32.7	121.8 ± 34.8	124.9 ± 35.7	118.2 ± 35.7	0.05	123.3 ± 33.0	121.5 ± 33.2	120.1 ± 35.5	125.8 ± 38.2	0.08
CRP (mg/L)	3.3 ± 4.0	3.7 ± 5.8	4.0 ± 6.2	5.0 ± 6.7	6.7 ± 9.7	7.9 ± 9.0	5.5 ± 10.3	<0.001	4.2 ± 6.3	4.6 ± 5.9	6.1 ± 8.8	8.1 ± 10.6	<0.001
Creatinine (mg/L)	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	1.3 ± 0.5	1.3 ± 0.9	<0.001	0.9 ± 0.2	0.8 ± 0.2	0.9 ± 0.3	1.3 ± 0.9	<0.001
Cystatin C (mg/L)	0.7 ± 0.05	0.8 ± 0.04	0.9 ± 0.05	1 ± 0.07	1.3 ± 0.1	1.7 ± 0.2	2.4 ± 0.3	<0.001	0.9 ± 0.2	1.0 ± 0.3	1.0 ± 0.3	1.4 ± 0.6	<0.001
eGFR _{cr} (mL/min/1.73 m ²) ^a	99.1 ± 11.7	91.6 ± 11.5	85.8 ± 11.6	78.4 ± 12.7	68.6 ± 14.9	55.2 ± 20.6	69.4 ± 26.2	<0.001	84.9 ± 14.3	85.0 ± 15.0	81.5 ± 19.7	68.6 ± 28.6	<0.001
ACR (mg/g)	3.5 [1.2-7.5]	3.2 [1.5-6.3]	3.6 [1.7-7.0]	3.8 [1.9-8.0]	4.9 [2.3-15.8]	13.3 [3.7-95.7]	5.6 [3.3-23.1]	<0.001	2.9 [1.4-4.8]	14.7 [11.8-19.7]	62.1 [42.0-119.0]	628.4 [423.8-1,138.2]	<0.001

Note: Values for continuous variables expressed as mean ± standard deviation or median [25th-75th percentile]; values for categorical variables expressed as proportion. Conversion factors for units: creatinine in mg/dL to mol/L, ×88.4; cholesterol in mg/dL to mmol/L, ×0.02586.

Abbreviations: ACR, albumin-creatinine ratio; BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; eGFR_{cr}, creatinine-based estimated glomerular filtration rate; eGFR_{cys}, cystatin C-based estimated glomerular filtration rate; LDL, low-density lipoprotein; NA, not applicable.

^aCalculated with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

Table 2

Prevalence of Albuminuria in Each Category of eGFR_{cys}

eGFR _{cys} (mL/min/1.73 m ²)	Urine Albumin-Creatinine Ratio (mg/g)			
	<10	10-29	30-299	300
Overall	698 (79)	118 (13)	60 (7)	9 (1)
105	1,853 (84)	243 (11)	92 (4)	12 (1)
90-104	3,116 (84)	391 (10)	187 (5)	36 (1)
75-89	2,018 (80)	306 (12)	178 (7)	30 (1)
60-74	512 (67)	123 (16)	91 (12)	38 (5)
45-59	73 (46)	26 (17)	34 (22)	24 (15)
30-44	86 (64)	17 (13)	11 (8)	21 (16)
15-29	8,356 (80)	1,224 (12)	653 (6)	170 (2)
Overall	10,403			

Note: Values given as number (percentage).

Abbreviation: eGFR_{cys}, cystatin C–based estimated glomerular filtration rate.

Table 3

Adjusted Hazard Ratios for the Composite Outcome by eGFR_{cys} and ACR Categories

eGFR _{cys} (mL/min/1.73 m ²)	ACR (mg/g)				
	<10	10-29	30-299	300	Overall
105	1.00 (0.80-1.26)	1.08 (0.71-1.66)	0.89 (0.49-1.63)	6.33 (2.60-15.40)	0.96 (0.79-1.17)
90-104	1.00 (reference)	1.14 (0.84-1.55)	1.53 (1.02-2.29)	2.12 (0.94-4.79)	1.00 (reference)
75-89	1.13 (0.98-1.31)	1.57 (1.25-1.96)	1.6 (1.21-2.11)	3.18 (2.07-4.88)	1.17 (1.04-1.33)
60-74	1.28 (1.10-1.49)	1.82 (1.45-2.29)	2.02 (1.57-2.59)	2.81 (1.76-4.50)	1.37 (1.20-1.56)
45-59	1.66 (1.36-2.02)	2.43 (1.82-3.23)	2.85 (2.13-3.82)	2.44 (1.58-3.75)	1.85 (1.58-2.18)
30-44	1.98 (1.35-2.92)	2.51 (1.49-4.25)	4.37 (2.94-6.48)	5.13 (3.24-8.13)	2.73 (2.16-3.46)
15-29	2.68 (1.84-3.92)	2.29 (1.08-4.86)	2.83 (1.33-6.02)	6.02 (3.56-10.17)	2.89 (2.19-3.82)
Overall	1.00 (reference)	1.34 (1.20-1.50)	1.64 (1.44-1.87)	2.73 (2.23-3.34)	

Note: Values given are hazard ratio (95% confidence interval). All hazard ratios adjusted for age, race, sex, total cholesterol level, diabetes, prevalent coronary heart disease, current smoking, hypertension, high-sensitivity C-reactive protein level, and body mass index.

Abbreviations: ACR, albumin-creatinine ratio; eGFR_{cys}, cystatin C–based estimated glomerular filtration rate.

Table 4Adjusted Hazard Ratios for All-Cause Mortality by eGFR_{cys} and ACR Categories

eGFR _{cys} (mL/min/1.73 m ²)	ACR (mg/g)				
	<10	10-29	30-299	300	Overall
105	0.93 (0.68-1.27)	0.95 (0.51-1.75)	0.59 (0.22-1.59)	4.44 (1.63-12.07)	0.86 (0.65-1.12)
90-104	1.00 (reference)	1.19 (0.80-1.77)	1.51 (0.89-2.57)	3.32 (1.35-8.15)	1.00 (reference)
75-89	1.05 (0.87-1.27)	1.45 (1.07-1.97)	1.89 (1.34-2.66)	3.71 (2.17-6.34)	1.11 (0.94-1.31)
60-74	1.16 (0.94-1.42)	1.99 (1.49-2.66)	2.02 (1.47-2.77)	2.33 (1.22-4.44)	1.28 (1.07-1.53)
45-59	1.73 (1.34-2.23)	2.21 (1.54-3.18)	3.35 (2.38-4.71)	2.94 (1.74-4.95)	1.94 (1.58-2.38)
30-44	2.44 (1.52-3.91)	3.35 (1.88-5.96)	4.97 (3.14-7.85)	4.65 (2.67-8.09)	3.17 (2.39-4.20)
15-29	3.27 (2.05-5.23)	3.37 (1.48-7.65)	4.37 (1.91-9.97)	8.01 (4.61-13.89)	7.93 (3.50-17.94)
Overall	1.00 (reference)	1.44 (1.24-1.67)	1.91 (1.62-2.25)	3.32 (2.62-4.20)	

Note: Values given are hazard ratio (95% confidence interval). All hazard ratios adjusted for age, race, sex, total cholesterol level, diabetes, prevalent coronary heart disease, current smoking, hypertension, high-sensitivity C-reactive protein level, and body mass index.

Abbreviations: ACR, albumin-creatinine ratio; eGFR_{cys}, cystatin C–based estimated glomerular filtration rate.

Table 5
Adjusted Hazard Ratios for Coronary Heart Disease by eGFR_{cys} and ACR Categories

eGFR _{cys} (mL/min/1.73 m ²)	ACR (mg/g)				
	<10	10-29	30-299	300	Overall
105	0.97 (0.70-1.37)	0.58 (0.26-1.32)	0.63 (0.23-1.72)	3.75 (1.18-11.91)	0.87 (0.65-1.18)
90-104	1.00 (reference)	1.10 (0.70-1.75)	1.54 (0.85-2.78)	1.29 (0.18-9.24)	1.00 (reference)
75-89	1.12 (0.91-1.39)	1.89 (1.38-2.58)	0.87 (0.51-1.50)	1.68 (0.74-3.84)	1.15 (0.96-1.39)
60-74	1.45 (1.16-1.81)	1.44 (0.98-2.11)	1.60 (1.06-2.43)	1.16 (0.42-3.16)	1.39 (1.14-1.70)
45-59	1.60 (1.16-2.19)	1.86 (1.12-3.07)	2.01 (1.20-3.36)	1.29 (0.60-2.78)	1.59 (1.22-2.06)
30-44	1.36 (0.66-2.80)	2.50 (1.01-6.15)	2.70 (1.25-5.83)	4.18 (2.11-8.28)	2.18 (1.45-3.26)
15-29	1.73 (0.85-3.55)	1.50 (0.37-6.09)	1.53 (0.21-10.99)	4.07 (1.78-9.29)	4.41 (1.09-17.82)
Overall	1.00 (reference)	1.22 (1.02-1.46)	1.15 (0.91-1.45)	1.76 (1.25-2.46)	

Note: Values given are hazard ratio (95% confidence interval). All hazard ratios adjusted for age, race, sex, total cholesterol level, diabetes, prevalent coronary heart disease, current smoking, hypertension, high-sensitivity C-reactive protein level, and body mass index.

Abbreviations: ACR, albumin-creatinine ratio; eGFR_{cys}, cystatin C–based estimated glomerular filtration rate.

Table 6

Adjusted Hazard Ratios for Heart Failure by eGFR_{cys} and ACR Categories

eGFR _{cys} (mL/min/1.73 m ²)	ACR (mg/g)				
	<10	10-29	30-299	300	Overall
105	1.12 (0.73-1.71)	1.92 (1.02-3.64)	2.10 (1.01-4.38)	19.60 (7.84-48.99)	1.29 (0.93-1.81)
90-104	1.00 (reference)	1.20 (0.69-2.09)	1.32 (0.60-2.87)	4.26 (1.54-11.77)	1.00 (reference)
75-89	1.13 (0.85-1.49)	1.84 (1.23-2.75)	2.17 (1.36-3.44)	3.43 (1.64-7.15)	1.24 (0.98-1.57)
60-74	1.50 (1.13-1.99)	2.00 (1.33-3.02)	2.89 (1.94-4.30)	6.82 (3.67-12.68)	1.68 (1.32-2.14)
45-59	1.92 (1.36-2.72)	3.30 (2.09-5.20)	5.56 (3.67-8.43)	6.25 (3.64-10.75)	2.65 (2.02-3.49)
30-44	2.66 (1.43-4.94)	5.18 (2.36-11.37)	8.28 (4.52-15.16)	13.97 (7.81-24.98)	5.02 (3.49-7.22)
15-29	3.57 (1.89-6.77)	1.18 (0.16-8.51)	1.34 (0.18-9.70)	7.98 (3.46-18.41)	26.47 (10.7-65.49)
Overall	1.00 (reference)	1.50 (1.24-1.82)	2.29 (1.87-2.80)	5.31 (4.08-6.91)	

Note: Values given are hazard ratio (95% confidence interval). All hazard ratios adjusted for age, race, sex, total cholesterol level, diabetes, prevalent coronary heart disease, current smoking, hypertension, high-sensitivity C-reactive protein level, and body mass index.

Abbreviations: ACR, albumin-creatinine ratio; eGFR_{cys}, cystatin C–based estimated glomerular filtration rate.