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Association of Intra-individual Differences in Estimated GFR by Creatinine Versus Cystatin C With Incident Heart Failure

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Abstract

Rationale & Objective: Lower estimated glomerular filtration rate (eGFR) is associated with heart failure (HF) risk. However, eGFR based on cystatin C (eGFRcys) and creatinine (eGFRcr) may differ substantially within an individual. The clinical implications of these differences for risk of HF among persons with chronic kidney disease (CKD) are unknown.

Study Design: Prospective cohort study.

Setting & Participants: 4,512 adults with CKD and without prevalent HF who enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Exposure: $eGFRdiff_{cys\text{-}cr}$ (eGFRcys minus eGFRcr).

Outcome: Incident HF hospitalization.

Analytical Approach: Fine-Gray proportional subhazards regression was used to investigate the associations of baseline, time-updated, and slope of $eGFRdiff_{cys\text{-}cr}$ with incident HF.

Results: Of 4,512 participants, one-third had eGFRcys and eGFRcr values that differed by over 15 mL/min/1.73 m^2. In multivariable-adjusted models, each 15 mL/min/1.73 m^2 lower baseline $eGFRdiff_{cys\text{-}cr}$ was associated with higher risk of incident HF hospitalization (hazard ratio [HR]=1.20; 95% CI: 1.07-1.34). In time-updated analyses, those with $eGFRdiff_{cys\text{-}cr} < -15$ had higher risk of incident HF hospitalization (HR=1.99; 95% CI: 1.39-2.86) and those with $eGFRdiff_{cys\text{-}cr} \geq 15$ had lower risk of incident HF hospitalization (HR=0.67; 95% CI: 0.49-0.91) compared to participants with similar eGFRcys and eGFRcr. Participants with faster declines in eGFRcys relative to eGFRcr had higher risk of incident HF (HR=1.49; 95% CI: 1.19-1.85) compared with those in whom eGFRcys and eGFRcr declined in parallel.

Limitations: Entry into the CRIC Study was determined by eGFRcr, which constrained the range of baseline eGFRcr but not of eGFRcys values.

Conclusions: Among persons with CKD who have large differences between eGFRcys and eGFRcr, risk for incident HF is more strongly associated with eGFRcys. Diverging slopes between eGFRcys and eGFRcr over time are also independently associated with risk of incident HF.

Plain Language Summary:

Individuals with lower kidney function, as determined by estimated glomerular filtration rate (eGFR), have higher risk of developing heart failure (HF). Cystatin C and creatinine are both biomarkers used to determine eGFR. However, cystatin C-based eGFR (eGFRcys) may differ substantially from creatinine-based eGFR (eGFRcr) within one individual. When these differences, $eGFRdiff_{cys\text{-}cr}$, are large, which eGFR measure is a more reliable indicator of HF risk is unclear. We analyzed the association of $eGFRdiff_{cys\text{-}cr}$, with risk of incident HF among an ambulatory CKD cohort. Among participants who have large differences between eGFRcys and eGFRcr, eGFRcys was more strongly associated with risk of incident HF . Evaluating both eGFRcys, eGFRcr, and their difference can optimize HF risk assessment among persons with CKD.

Keywords

chronic kidney disease; heart failure; cystatin C; creatinine; estimated glomerular filtration rate

Introduction

Patients with chronic kidney disease (CKD) are at particularly high risk for developing heart failure (HF). [1,2] Lower estimated glomerular filtration rate (eGFR) is strongly and independently associated with risk of HF events.[3,4] Individual patients may have very different eGFR values depending on whether creatinine or cystatin C is used for the estimation.[5–8] Although cystatin C has repeatedly been shown to have stronger and more linear associations with incident HF compared to creatinine,[4,9–13] creatinine-based estimated glomerular filtration rate (eGFRcr) is far more widely used in clinical practice than cystatin C-based eGFR (eGFRcys).

Use of eGFRcr may lead to inaccurate estimates of kidney function because creatinine is heavily influenced by non-kidney factors, including physical activity, muscle mass, diet, and health status.[14–19] This is a concern particularly among patients with CKD, who often experience sarcopenia and frailty.[20,21] Recently, the National Kidney Foundation (NKF) and American Society of Nephrology (ASN) recommended increased use of cystatin C to estimate kidney function because cystatin C is less influenced than creatinine by these common non-kidney factors and is unaffected by race or genetic ancestry.[22–24] As health systems increasingly adopt cystatin C, large, within-individual differences between eGFRcys and eGFRcr will become widely recognized, particularly when non-kidney factors disproportionately affect eGFRcr.[5–8]

Prior studies conducted among population-based cohorts or clinical trials have found associations of these differences, defined as $eGFRdiff_{cys\text{-}cr}$ = eGFRcys minus eGFRcr, with all-cause mortality, falls, hospitalizations, atherosclerotic cardiovascular disease (CVD) events, and end-stage kidney disease (ESKD).[5,6,25,26] However, the associations of $eGFRdiff_{cys\text{-}cr}$ with HF hospitalizations have not been evaluated among a cohort with established CKD. Furthermore, few prior studies have investigated the clinical interpretation of changes in $eGFRdiff_{cys\text{-}cr}$ over time, which result from differing rates of eGFRcys versus eGFRcr decline during longitudinal follow-up.[26] Elucidating the associations of $eGFRdiff_{cys\text{-}cr}$ with HF risk is an important area of investigation because HF is the most common cardiovascular complication among persons with reduced eGFR.[10,27,28]

We analyzed data from a large multi-center study of participants with mild to moderate CKD to answer three questions: 1) Among individuals without prevalent HF at baseline, is baseline $eGFRdiff_{cys\text{-}cr}$ independently associated with incident HF hospitalization?; 2) Does the inclusion of time-updated measures yield stronger associations between $eGFRdiff_{cys\text{-}cr}$ and incident HF?; and 3) Is widening or narrowing of $eGFRdiff_{cys\text{-}cr}$ over time independently associated with incident HF?

Methods

Study design and population

The Chronic Renal Insufficiency Cohort (CRIC) Study is a multicenter observational cohort study that enrolled 5,499 adults from seven clinical centers across the U.S., representing a broad range of age, race, ethnicity, diabetes status, and severity of kidney disease.[29–31] Participants had eGFRcr of 20-70 mL/min/1.73 m^2.[32] Medical history, medication use, and clinical events were updated semi-annually. Laboratory testing was conducted annually. Additional details on study design, study population, and participant characteristics have been published previously.[29–31] Participants provided written informed consent, and the study protocol was approved by the institutional review boards at each participating site. In the present analysis, we excluded 543 participants who did not have simultaneous serum cystatin C and creatinine measurements from at least two study visits within the first three years of follow-up. A further 444 participants with self-reported prevalent HF at baseline were excluded.

Data were obtained from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) repository in April 2021 This current study was determined to be exempt from review by the University of California, San Francisco IRB, as all data were de-identified.

Predictor

Our predictor of interest, $eGFRdiff_{cys\text{-}cr}$, was defined as eGFRcys minus eGFRcr and analyzed as a baseline, time-updated, and longitudinal predictor. Serum cystatin C and creatinine levels were measured annually in the CRIC Study and applied to the 2012 and 2021 CKD Epidemiology Collaboration (CKD-EPI) race-free equations, respectively.[22,33] Additional details regarding cystatin C and creatinine assays are in the Supplemental Methods.

Outcomes

The outcome was incident HF hospitalization, defined as first hospitalization for HF. At least two study physicians reviewed all possible HF events using medical records, adjudicating based on clinical symptoms, radiographic evidence of pulmonary congestion, physical examination, and when available, central venous hemodynamic monitoring data and echocardiographic imaging. HF was confirmed when both physician adjudicators agreed upon a “probable” or “definite” HF event based on modified clinical Framingham criteria.[34] Hospitalizations for HF were adjudicated from study entry until administrative censoring in 2018. Additional details regarding adjudication of HF events are included in the Supplemental Methods.

Covariates

All covariates were obtained at the baseline study visit concurrently with serum cystatin C and creatinine. Demographic characteristics, medical history, and medication use were self-reported. Race or ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Hispanic, or other. Specific covariate definitions are included in the Supplemental Methods.

Statistical analysis

We summarized baseline characteristics, overall and stratified by three $eGFRdiff_{cys\text{-}cr}$ categories: < −15 (eGFRcys lower than eGFRcr), −15 to 15 (eGFRcys similar to eGFRcr), and ≥15 mL/min/1.73 m^2 (eGFRcys higher than eGFRcr). These $eGFRdiff_{cys\text{-}cr}$ cutoffs were chosen because 15 mL/min/1.73 m^2 corresponds to approximately 1-standard deviation (SD) of baseline $eGFRdiff_{cys\text{-}cr}$, represents a clinically meaningful difference in eGFR that defines CKD stages, and has been used in prior studies to categorize $eGFRdiff_{cys\text{-}cr}$.[5,6,35]

To investigate the association between baseline $eGFRdiff_{cys\text{-}cr}$ and incident HF hospitalization, we applied Fine-Gray proportional subhazards regression, with death modeled as a competing risk.[36] We analyzed $eGFRdiff_{cys\text{-}cr}$ separately as a continuous and categorical predictor; we scaled $eGFRdiff_{cys\text{-}cr}$ per 15 mL/min/1.73 m^2 and compared $eGFRdiff_{cys\text{-}cr}$ categories to the reference group of $eGFRdiff_{cys\text{-}cr}$ between −15 to 15 mL/min/1.73 m^2. We initially adjusted for age, sex, race or ethnicity, and baseline eGFRcr. We adjusted for eGFRcr to assess the prognostic value of $eGFRdiff_{cys\text{-}cr}$ independent of the most common measure of kidney function in current clinical practice. Our multivariable adjusted model included SBP; type 2 diabetes (DM2); CVD; current smoking; UPCR; BMI; and use of statins, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (ACEIs/ARBs), diuretics, and beta-blockers. In exploratory analyses, we additionally adjusted for steroid use, serum albumin, hemoglobin, and C-reactive protein (CRP) concentrations to determine whether these markers of health status would attenuate the associations of $eGFRdiff_{cys\text{-}cr}$ with incident HF hospitalization. We log-transformed UPCR and CRP to correct their right-skewed distributions. We censored participants at time of ESKD since incident ESKD increases risk of hospitalization for fluid overload, which may be a result of inadequate fluid removal during dialysis rather than incident HF.

Next, we extended the baseline models by including time-updated $eGFRdiff_{cys\text{-}cr}$ values from the first three annual study visits and repeated the Fine-Gray analyses. The first three annual study visits were selected to provide a sufficient number of $eGFRdiff_{cys\text{-}cr}$ values for evaluation of time-updated $eGFRdiff_{cys\text{-}cr}$, while limiting the potential impact of participant loss to follow-up. We adjusted for time-updated measures of kidney function, including eGFRcr and UPCR. Because time-updated SBP is associated with progression of CKD[37] and weight loss becomes increasingly prevalent as CKD progresses,[38] we also adjusted for time-updated SBP and BMI as important potential confounders.

During longitudinal follow-up, slopes of eGFRcys and eGFRcr may diverge; we represented this using slope of $eGFRdiff_{cys\text{-}cr}$. To determine the association of $eGFRdiff_{cys\text{-}cr}$ slope with incident HF hospitalization, we used a joint model to simultaneously evaluate repeated measures of $eGFRdiff_{cys\text{-}cr}$ and time-to-event data.[39] Through our joint models,[26] we obtained within-subject estimates of longitudinal $eGFRdiff_{cys\text{-}cr}$ intercept and slope. We analyzed $eGFRdiff_{cys\text{-}cr}$ slope as a continuous variable and created tertiles of $eGFRdiff_{cys\text{-}cr}$ slope. In the first tertile, eGFRcys declined more quickly than eGFRcr over time, resulting in the most negative $eGFRdiff_{cys\text{-}cr}$ slopes. The second tertile served as the reference group and comprised individuals with eGFRcys and eGFRcr that declined approximately in parallel. In the third tertile, eGFRcr declined more quickly than eGFRcys, which is represented by the

most positive $eGFRdiff_{cys\text{-}cr}$ slopes. We evaluated these tertiles as predictors of incident HF hospitalizations in Fine-Gray models.

We conducted secondary analyses to further understand the association of $eGFRdiff_{cys\text{-}cr}$ with incident HF. First, we individually modeled the associations of eGFRcys, eGFRcr, and eGFR using the combined creatinine and cystatin C equation (eGFRcombined)[22] with incident HF. Next, we compared the associations of eGFRcys versus eGFRcr with incident HF by including both eGFR values in the same multivariable-adjusted model. We then modeled the association of slopes of eGFRcys and eGFRcr individually and jointly. We also explored whether associations between $eGFRdiff_{cys\text{-}cr}$ and outcomes differed by a select set of baseline characteristics through stratified analyses and tests for interactions of $eGFRdiff_{cys\text{-}cr}$ with each baseline characteristic. The a *priori* selected baseline characteristics included age < or ≥ 60 years, female or male sex, self-identified Black or non-Black race, eGFRcr < or ≥ 45 mL/min/1.73 m^2, and albumin < or ≥ 3.5 g/dL. Lastly, we repeated our baseline, time-updated, and slope analyses adjusting for eGFRcys rather than eGFRcr.

In sensitivity analyses, we first excluded the participants who self-reported steroid use at the baseline visit and repeated our baseline, time-updated, and slope analyses. We then performed the same sensitivity analysis after excluding participants who experienced an incident HF hospitalization prior to their third annual study visit, the final study visit when $eGFRdiff_{cys\text{-}cr}$ was time-updated.

Examination of variance inflation factor and condition index diagnostics found no evidence of collinearity between covariates in our models. Proportional hazards assumptions were assessed using Schoenfeld residuals. All baseline variables had <2% missing except for UPCR (5%) and CRP (28%). We performed multiple imputation using SAS Proc MI. The Markov chain Monte Carlo method for arbitrary missing multivariate normal data was used to impute missing covariates, with 20 imputations to ensure ~95% relative efficiency. All tests were two-tailed with a statistical significance level of $P < 0.05$. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc) and R, version 4.1.0 (R Foundation for Statistical Computing).

Results

Among 4,512 CRIC Study participants, 1981 (44%) were women, 1906 (42%) were non-Hispanic Black, and 447 (11%) were Hispanic. Mean age was 59.4 years, eGFRcys was 55 mL/min/1.73 m^2, and eGFRcr was 49 mL/min/1.73 m^2 (Table 1 and Figure 1). Baseline $eGFRdiff_{cys\text{-}cr}$ ranged from −52 to 65 mL/min/1.73 m^2, with a mean of 6 and SD of 16. Approximately two-thirds of participants had a baseline $eGFRdiff_{cys\text{-}cr}$ between −15 and 15 mL/min/1.73 m^2 (mid-range $eGFRdiff_{cys\text{-}cr}$); 7% had an $eGFRdiff_{cys\text{-}cr} < -15$ (negative $eGFRdiff_{cys\text{-}cr}$) and 26% had an $eGFRdiff_{cys\text{-}cr} \geq 15$ (positive $eGFRdiff_{cys\text{-}cr}$) (Table 1). Participants within the negative $eGFRdiff_{cys\text{-}cr}$ group were generally older and had the highest prevalence of diabetes and CVD compared with those in the other two $eGFRdiff_{cys\text{-}cr}$ groups; conversely, participants with positive $eGFRdiff_{cys\text{-}cr}$ were younger and had lower prevalence of baseline comorbidities and medication use.

Association of baseline eGFRdiff$_{cys-cr}$ with incident HF

A total of 532 (12%) participants developed incident HF, with median time until incident HF hospitalization of 3.5 years (IQR: 1.5-7.1). After adjusting for demographic characteristics and eGFRcr, each 15 mL/min/1.73 m^2 lower baseline eGFRdiff$_{cys-cr}$ was associated with 56% higher risk of incident HF (Table 2). Further multivariable adjustment attenuated this association to 20%. The crude rate of incident HF was highest among participants with negative eGFRdiff$_{cys-cr}$ and lowest among participants with positive eGFRdiff$_{cys-cr}$ (Figure 2A). Compared to the mid-range eGFRdiff$_{cys-cr}$ group, positive and negative eGFRdiff$_{cys-cr}$ categories were not statistically significantly associated with multivariable adjusted risk of incident HF (Table 2).

Association of time-updated eGFRdiff$_{cys-cr}$ with incident HF

In multivariable adjusted models accounting for time-updated eGFRdiff$_{cys-cr}$ and covariates, each 15 mL/min/1.73 m^2 lower baseline eGFRdiff$_{cys-cr}$ was associated with 36% higher risk of incident HF (Table 2). Compared to participants with mid-range eGFRdiff$_{cys-cr}$, participants in the negative eGFRdiff$_{cys-cr}$ category had a higher adjusted risk of incident HF (sHR 1.99, 95% CI 1.39-2.86), and those in the positive eGFRdiff$_{cys-cr}$ group had a lower adjusted risk of incident HF (sHR 0.67, 95% CI 0.49-0.91) (Table 2). These results were only modestly attenuated by further adjustment for markers of nutritional status and inflammation (Table S1).

Association of eGFRdiff$_{cys-cr}$ slope with incident HF

Slopes of eGFRdiff$_{cys-cr}$ were derived using a median of four annual eGFRdiff$_{cys-cr}$ values (IQR: 3-4). The mean (SD) annual change in eGFRdiff$_{cys-cr}$ was −0.4 (0.9) mL/min/1.73 m^2 per year. The correlation coefficient between baseline eGFRdiff$_{cys-cr}$ and eGFRdiff$_{cys-cr}$ slope was −0.15 ($p<0.001$). In multivariable models including adjustment for baseline eGFRdiff$_{cys-cr}$, each SD lower eGFRdiff$_{cys-cr}$ slope was associated with 37% higher risk of incident HF (Table 2). Participants within the first tertile of eGFRdiff$_{cys-cr}$ slope had the steepest declines in eGFRcys relative to eGFRcr and had the highest crude rate of incident HF hospitalizations (Figure 2B). In multivariable adjusted models, risk of incident HF hospitalization was 49% higher among participants in the first tertile compared to the middle tertile of eGFRdiff$_{cys-cr}$ slope. Those in the third tertile had steeper declines in eGFRcr than eGFRcys and had 21% lower risk of incident HF hospitalization, although the finding did not reach statistical significance (Table 2). Despite this risk gradient across tertiles of eGFRdiff$_{cys-cr}$ slope, mean eGFRcr slope was similar in each tertile (range −1.9 and −1.5 mL/min/1.73 m^2/year). Conversely, mean eGFRcys slope was substantially more negative in the lowest tertile of eGFRdiff$_{cys-cr}$ and more positive in the highest (range −3.2 and 0.4 mL/min/1.73 m^2/year). Similar to the time-updated analyses, these eGFRdiff$_{cys-cr}$ slope analyses were unaffected by additional adjustment for potential confounders or mediators (Table S1).

Secondary analyses

All three eGFR measures, eGFRcys, eGFRcr, and eGFRcombined, were associated with incident HF when modeled individually in multivariable-adjusted models (Table S2).

However, when eGFRcys and eGFRcr were both included in the same multivariable-adjusted model, only eGFRcys was associated with incident HF. (Table S2). Similarly, only slope of eGFRcys remained associated with the incident HF when the slopes of eGFRcys and eGFRcr were jointly modeled (Table S3).

There was no evidence of that age < or ≥ 60 years, female or male sex, self-identified Black or White race, eGFRcr < or ≥ 45, or serum albumin < or ≥ 3.5 g/dL modified the association between $eGFRdiff_{cys\text{-}cr}$ with incident HF hospitalization in time-updated subgroup analyses (Table S4). Adjusting for eGFRcys rather than eGFRcr in our multivariable models revealed that $eGFRdiff_{cys\text{-}cr}$ was no longer associated with incident HF in baseline and time-updated analyses; however, the slope of $eGFRdiff_{cys\text{-}cr}$ remained independently associated with incident HF even after adjustment for eGFRcys (Table S5). The results from our analyses were unaffected by the exclusion of 563 participants who reported steroid use at baseline (Table S6) nor by the exclusion of 220 participants who experienced incident HF hospitalization prior to the third annual study visit (Table S7).

Discussion

In this diverse, multicenter cohort of adults with CKD, we found that differences between eGFRcys and eGFRcr were associated with risk of incident HF hospitalization. At baseline, lower $eGFRdiff_{cys\text{-}cr}$ was associated with higher risk of incident HF in multivariable analyses including eGFRcr. In time-updated analyses, participants with a negative $eGFRdiff_{cys\text{-}cr}$ (eGFRcys lower than eGFRcr) had double the risk of incident HF hospitalization compared to those in whom eGFRcys and eGFRcr were similar. Conversely, those with positive $eGFRdiff_{cys\text{-}cr}$ (eGFRcys higher than eGFRcr) had 33% lower risk of incident HF hospitalization. Longitudinal slope analyses revealed that participants with eGFRcys that declined more quickly than eGFRcr had significantly higher risk of incident HF, even in adjusted analyses. Taken together, our study provides evidence that intra-individual differences between eGFRcys and eGFRcr at baseline and longitudinally provide important prognostic information regarding risk of incident HF among individuals with CKD. Furthermore, risk for incident HF appears to be driven by eGFRcys rather than by eGFRcr when the two are discrepant.

Impaired kidney function is a risk factor for incident HF.[1,11,40] Our findings and that of previous studies show that eGFRcys is more strongly and linearly associated with incident HF compared to eGFRcr.[1,4,9–13] However, prior studies compared the relative associations of eGFRcr and eGFRcys with incident HF at a *population* level rather than assessing the implications of different eGFR measurements in the same individual. We provide novel evidence that *intra-individual* differences between eGFRcys and eGFRcr and dynamic changes in these differences over time may inform an individual patient's risk for incident HF hospitalization. Compared to prior studies, our study can better inform the clinical interpretation of highly discrepant eGFRcys and eGFRcr values within an individual patient. While creatinine is currently the most commonly used biomarker to estimate glomerular filtration rate (GFR), recent national efforts to provide race-agnostic assessment of kidney function will likely galvanize increased use of cystatin C.[22–24] Where available, there is growing recognition that a large proportion of individuals have wide differences between

eGFRcys and eGFRcr, and that such intra-individual differences have strong relationships with adverse clinical outcomes.[5–7]

Large differences between eGFRcys and eGFRcr may occur when non-GFR factors—including physical activity, sarcopenia, and nutrition— differentially influence cystatin C and creatinine levels. These non-GFR factors are particularly important to consider in the evaluation of patients with CKD, as worsening kidney function leads to accelerated declines in health status, physical function, and muscle mass, which affect creatinine more so than cystatin C.[17] A few prior studies have assessed associations between baseline $eGFRdiff_{cys\text{-}cr}$ and clinical outcomes.[5,6,25] One of these studies evaluated HF as an outcome among a CKD population but had a relatively low event rate and found no association between baseline $eGFRdiff_{cys\text{-}cr}$ and HF hospitalization.[25] Our study comprised a greater number of incident HF events and found an association between baseline $eGFRdiff_{cys\text{-}cr}$ and incident HF when $eGFRdiff_{cys\text{-}cr}$ was evaluated as a continuous, but not categorical predictor. To better account for changes in health status that may differentially impact creatinine versus cystatin C during longitudinal follow-up, we modeled repeated measures of $eGFRdiff_{cys\text{-}cr}$ in both time-updated and slope analyses. We observed in time-updated analyses that $eGFRdiff_{cys\text{-}cr}$ categories clearly identified subgroups of individuals with CKD who are at lower or higher risk for incident HF. Analyses of $eGFRdiff_{cys\text{-}cr}$ slope revealed that diverging eGFRcys and eGFRcr values over time are also associated with incident HF. The associations elucidated by our time-updated and slope analyses would be missed by a single baseline assessment of $eGFRdiff_{cys\text{-}cr}$, as one $eGFRdiff_{cys\text{-}cr}$ value appears to incompletely capture the compounding impact of non-GFR factors on eGFRcr values over time. While non-GFR determinants of cystatin C — such as obesity, steroid use, and possibly inflammation — also exist, their combined effects on serum cystatin C levels are smaller in magnitude than the non-GFR determinants on serum creatinine.[41,42] As a result, our estimates remained robust and unchanged after controlling for BMI, steroid use, and CRP.

Our findings offer three major clinical implications. First, patients with CKD may commonly have large $eGFRdiff_{cys\text{-}cr}$; in these individuals, eGFRcr alone is likely not adequately capturing risk for HF, which is the most common cardiovascular outcome associated with CKD. A large $eGFRdiff_{cys\text{-}cr}$ should prompt clinicians to carefully consider whether creatinine may be biased by common factors unrelated to kidney function and to use eGFRcys as a more reliable indicator of HF risk. Although cystatin C might be the biased marker in some cases, our results indicate that clinical risk generally aligns more with cystatin C than creatinine. Second, the consistently stronger associations of time-updated and longitudinal $eGFRdiff_{cys\text{-}cr}$ with incident HF, relative to the associations of baseline $eGFRdiff_{cys\text{-}cr}$, demonstrate that repeating cystatin C annually may improve clinical risk assessment in patients with CKD. Third, our findings support reporting eGFRcys and eGFRcr separately because the difference between their values at baseline and during longitudinal follow-up provides important prognostic information that may be obscured if the eGFRcombined equation were to be used.[33]

The strengths of this study include repeated assessments of $eGFRdiff_{cys\text{-}cr}$ among a large, national CKD cohort with carefully adjudicated HF hospitalizations. We also acknowledge important limitations. First, entry into the CRIC Study was determined by eGFRcr, which

constrained the range of eGFRcr but not of eGFRcys. This likely excluded a preponderance of participants who would have been categorized into the negative $eGFRdiff_{cys\text{-}cr}$ groups relative to the number in the positive group at baseline. Second, we chose to use the absolute rather than relative difference between eGFRcys and eGFRcr because in our clinical experience, clinicians intuitively understand and can calculate the absolute difference between two eGFR values. We acknowledge that using absolute difference constrains the range of $eGFRdiff_{cys\text{-}cr}$ at lower eGFR values. Third, cystatin C was not calibrated to a traceable international standard. The CRIC Study internally calibrated cystatin C measures to correct for drift over time caused by using different calibrator and reagent lots. We expect that potential imprecision due to measurement error would be non-differential among $eGFRdiff_{cys\text{-}cr}$ categories or between individual participants, and any error would diminished the strength of our associations. Fourth, we did not have sufficient data on ejection fraction at the time of HF hospitalization to stratify outcomes by HF sub-types. Fifth, HF exacerbations that might have been diagnosed in the ambulatory care setting were not evaluated by the CRIC Study and thus would have been missed in our analyses. Sixth, we used a joint model to obtain within-subject estimates of $eGFRdiff_{cys\text{-}cr}$ slope.[39] While these are slope estimates with confidence intervals rather than actual $eGFRdiff_{cys\text{-}cr}$ slopes, the joint modeling approach reduces bias, accounts for informative censoring, and improves precision relative to more traditional survival analyses.[43–47] Furthermore, any measurement error in estimating slopes would be non-differential among $eGFRdiff_{cys\text{-}cr}$ categories or between individual participants and variance would tend to limit our ability to find associations. Lastly, our results may not generalize to persons without CKD or populations outside of the United States.

Our study showed that large differences between eGFRcys and eGFRcr convey important prognostic information regarding risk of incident HF hospitalization. During longitudinal follow-up, steeper declines in eGFRcys than eGFRcr portend higher risk of HF events. Thus, in patients with CKD, annual measures of serum creatinine and cystatin C and separate reporting of both eGFRcys and eGFRcr would optimize the assessment of HF risk.

Supplementary Material

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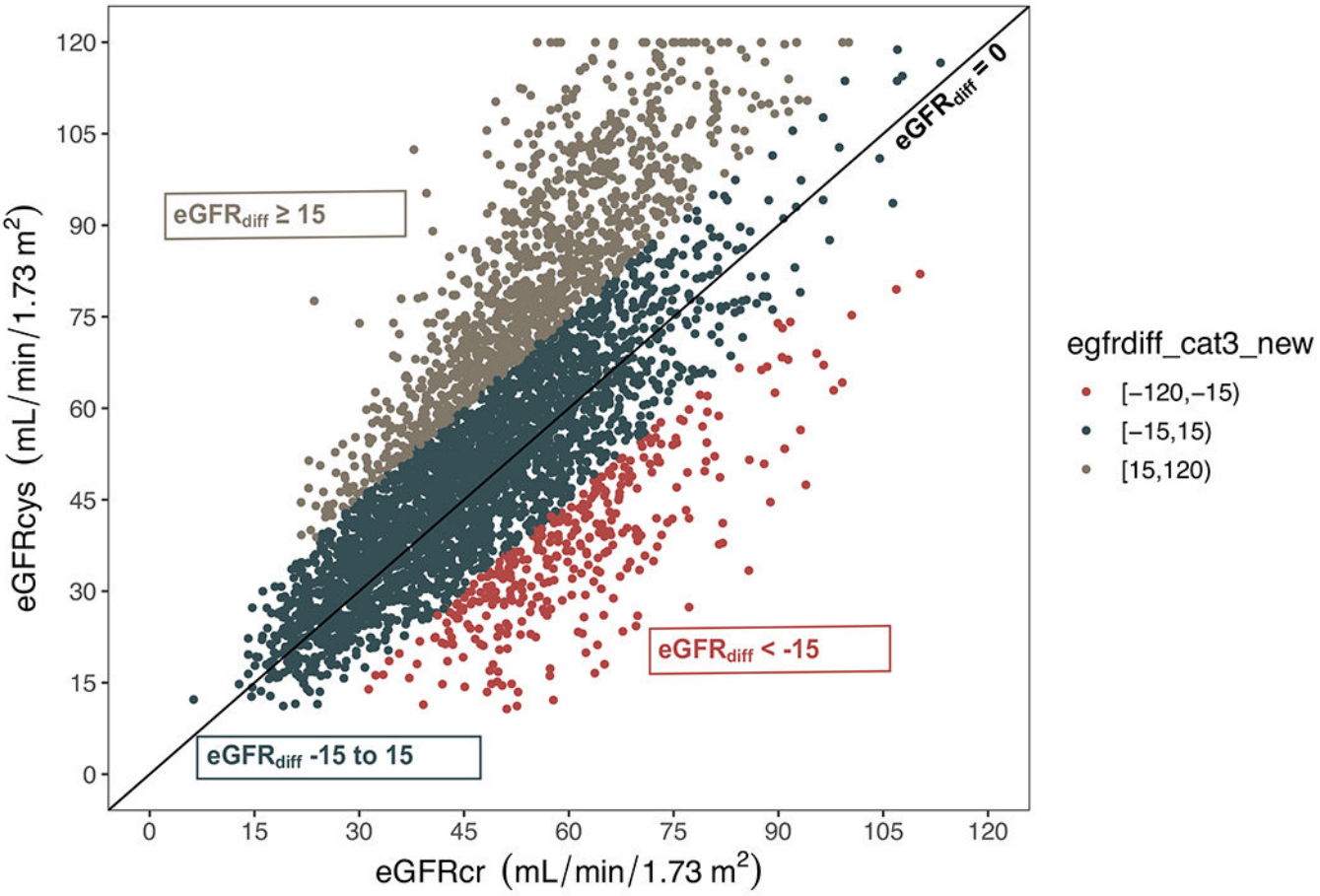

Figure 1.

Scatterplot of the relation between eGFRcys, eGFRcr, and $eGFRdiff_{cys-cr}$ at baseline

Colors indicate estimated glomerular filtration rate difference ($eGFRdiff_{cys-cr}$) category: red = $eGFRdiff_{cys-cr} < -15$, dark blue = $eGFRdiff_{cys-cr}$ −15 to 15, grey = $eGFRdiff_{cys-cr} \geq 15$. Diagonal line represents $eGFRdiff_{cys-cr}$ of zero.

Abbreviations: eGFRcys, cystatin C-based estimated glomerular filtration rate; eGFRcr, creatinine-based estimated glomerular filtration rate

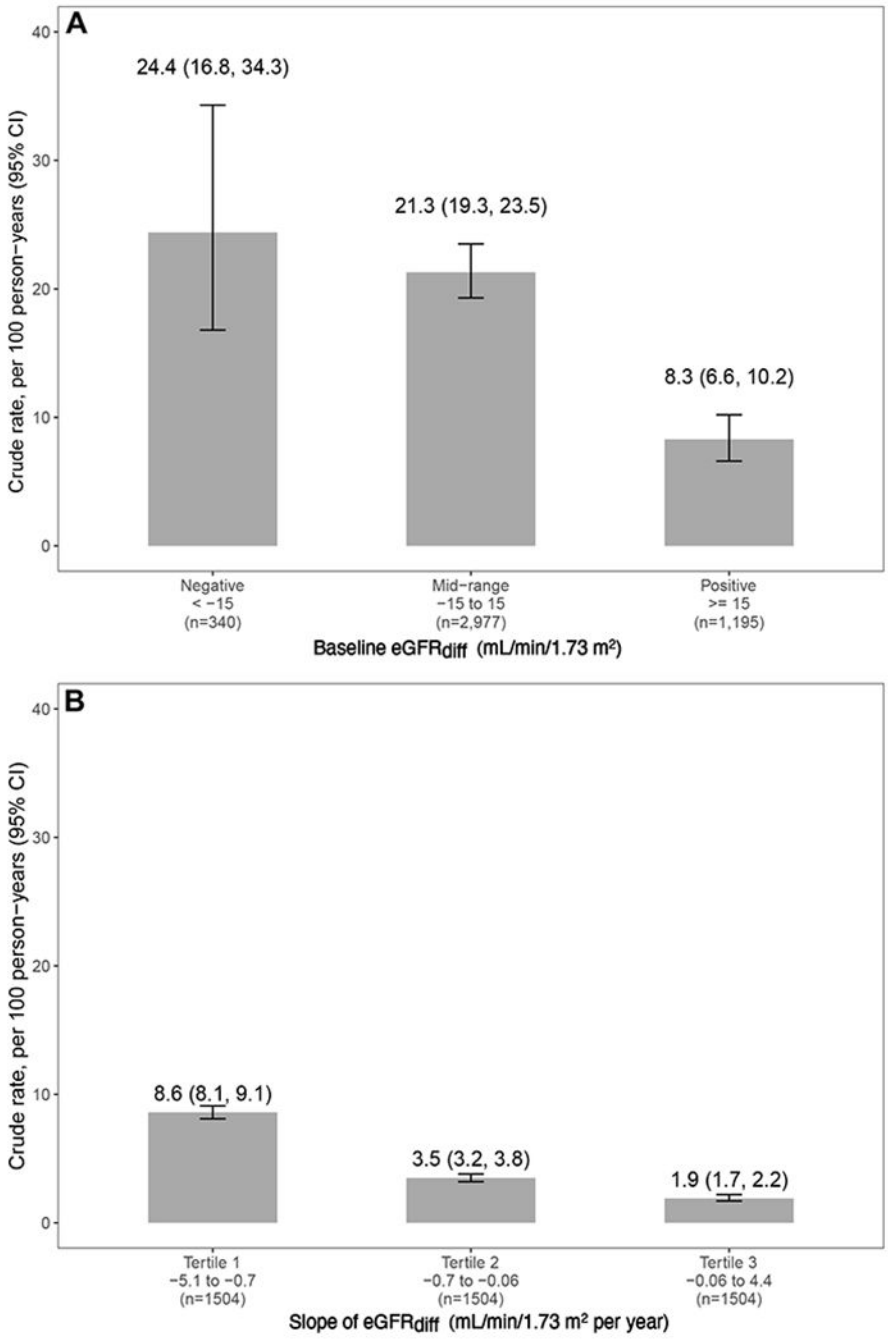

Figure 2.

Crude incidence rates of incident heart failure (HF) by baseline and slope of $eGFRdiff_{cys-cr}$ category among participants without prevalent HF at baseline (n=4512)

Table 1.

Baseline characteristics of participants without prevalent heart failure at baseline, by category of baseline $eGFRdiff_{cys-cr}$ in the Chronic Renal Insufficiency Cohort Study

Characteristics	Baseline $eGFRdiff_{cys-cr}$ (mL/min/1.73 m^2)			
	Negative < −15 (eGFRcys lower than eGFRcr)	Mid-range −15 to 15 (eGFRcys similar to eGFRcr)	Positive ≥ 15 (eGFRcys higher than eGFRcr)	Overall
Sample size	340	2,977	1,195	4,512
Demographics				
Age, yr, mean (SD)	62.9 (9.3)	59.8 (10.7)	57.4 (10.6)	59.4 (10.7)
Female sex, n (%)	130 (38.2)	1325 (44.5)	526 (44.0)	1981 (43.9)
Race/Ethnicity				
White, Non-Hispanic, n (%)	183 (53.8)	1294 (43.5)	487 (40.8)	1964 (43.5)
Black, Non-Hispanic, n (%)	111 (32.6)	1184 (39.8)	611 (51.1)	1906 (42.4)
Hispanic, n (%)	32 (9.2)	390 (13.1)	55 (4.6)	447 (10.6)
Other, n (%)	14 (4.1)	109 (3.7)	42 (3.5)	165 (3.7)
Comorbidities				
Diabetes, n (%)	199 (58.5)	1570 (52.7)	422 (35.3)	2191 (48.6)
Hypertension, n (%)	293 (86.4)	2666 (89.6)	900 (75.3)	3859 (85.5)
Cardiovascular disease, n (%)	106 (31.2)	844 (28.4)	231 (19.3)	1181 (26.2)
Smoker, n (%)	53 (15.6)	382 (12.8)	104 (8.7)	539 (11.9)
Systolic blood pressure, mm Hg mean (SD)	128.5 (19.0)	128.8 (21.0)	124.9 (20.2)	127.8 (20.7)
BMI, kg/m^2, mean (SD)	33.7 (8.3)	32.7 (7.7)	30.4 (6.1)	32.1 (7.4)
Medications, n (%)				
Statins	204 (60.2)	1758 (59.5)	558 (47.0)	2520 (56.3)
ACEI/ARB	240 (70.8)	2107 (71.3)	696 (58.5)	3043 (67.9)
Diuretics	156 (46.0)	1702 (57.6)	517 (43.5)	2375 (53.0)
Beta-blockers	163 (48.1)	1454 (49.2)	442 (37.2)	2059 (45.9)
Steroids	65 (19.2)	369 (12.5)	129 (10.8)	563 (12.6)
Laboratory values				
eGFRcys, mL/min/1.73 m^2, mean (SD)	37 (13)	47 (16)	81 (18)	55 (23)
eGFRcr, mL/min/1.73 m^2, mean (SD)	61 (14)	45 (15)	55 (13)	49 (16)

Characteristics	Baseline eGFRdiff$_{cys-cr}$ (mL/min/1.73 m^2)			
	Negative < −15 (eGFRcys lower than eGFRcr)	Mid-range −15 to 15 (eGFRcys similar to eGFRcr)	Positive ≥ 15 (eGFRcys higher than eGFRcr)	Overall
eGFRdiff$_{cys-cr}$, mL/min/1.73 m^2, mean (SD)	−24 (8)	2 (7)	26 (10)	6 (16)
UPCR, g/g, median (IQR)	0.20 (0.08 - 0.78)	0.20 (0.06 - 0.86)	0.07 (0.04 - 0.17)	0.14 (0.06 – 0.62)
Albumin, g/dL, mean (SD)	3.9 (0.5)	3.9 (0.5)	4.1 (0.4)	4.0 (0.5)
Hemoglobin, g/dL, mean (SD)	12.6 (1.8)	12.6 (1.8)	13.2 (1.6)	12.8 (1.7)
High-sensitivity CRP, mg/L, median (IQR)	4.6 (1.3 - 9.1)	2.8 (1.1 – 6.8)	1.7 (0.9 – 4.1)	2.5 (1.0 – 6.1)

Abbreviations: SD, standard deviation; IQR, interquartile range; eGFRdiff$_{cys-cr}$, estimated glomerular filtration rate difference; BMI, body mass index; ACEI/ARB, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; eGFRcys, cystatin C-based estimated glomerular filtration rate using the 2012 CKD-EPI equation; eGFRcr, creatinine-based estimated glomerular filtration rate using the 2021 CKD-EPI race-free equation; UPCR, urine protein-to-creatinine ratio; CRP, C-reactive protein.

Table 2.

Associations of baseline, time-updated, and slope of $eGFRdiff_{cys–cr}$ with risk of incident heart failure (HF) hospitalization among participants without prevalent HF at baseline (n=4512)

	Subhazard ratio (95% CI)	
	Demographic adjusted	**Multivariable adjusted**
Baseline measures		
Continuous $eGFRdiff_{cys-cr}$ (per 15 mL/min/1.73 m^2 lower)	1.56 (1.42, 1.71), p<0.001	1.20 (1.07, 1.34), p=0.003
Categorical $eGFRdiff_{cys-cr}$ (mL/min/1.73m^2)		
< −15	1.55 (1.06, 2.26), p=0.02	1.14 (0.77, 1.70), p=0.5
−15 to 15	Ref	Ref
≥ 15	0.53 (0.42, 0.68), p<0.001	0.78 (0.61, 1.01), p=0.06
Time-updated measures *		
Continuous $eGFRdiff_{cys-cr}$ (per 15 mL/min/1.73 m^2 lower)	1.69 (1.52, 1.88), p<0.001	1.36 (1.18, 1.55), p<0.001
Categorical $eGFRdiff_{cys-cr}$ (mL/min/1.73 m^2)		
<−15	2.71 (1.90, 3.88), p<0.001	1.99 (1.39, 2.86), p<0.001
−15 to 15	Ref	Ref
≥ 15	0.47 (0.35, 0.63), p<0.001	0.67 (0.49, 0.91), p=0.01
Slope of eGFRdiff † (mL/min/1.73 m^2 per year)		
Continuous slope of $eGFRdiff_{cys-cr}$ (per SD lower)	1.45 (1.30, 1.59), p<0.001	1.37 (1.23, 1.52), p<0.001
Tertile 1, −5.1 to −0.7	1.69 (1.37, 2.09), p<0.001	1.49 (1.19, 1.85), p<0.001
Tertile 2, −0.7 to −0.06	Ref	Ref
Tertile 3, −0.06 to 4.4	0.80 (0.62, 1.04), p=0.09	0.79 (0.61, 1.03), p=0.09

Demographic-adjusted models: adjusted for age, sex, race or ethnicity, and creatinine-based estimated glomerular filtration rate (eGFRcr)

Multivariable-adjusted models: adjusted for demographic-adjusted model and systolic blood pressure (SBP), type 2 diabetes, cardiovascular disease, current smoker, log(urine protein-to-creatinine ratio (UPCR)), body mass index (BMI), and use of statins, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, diuretics, or beta-blockers

*All covariates from baseline exam except eGFRcr, UPCR, BMI, SBP, and estimated glomerular filtration rate difference ($eGFRdiff_{cys-cr}$), which were time-updated.

†Within-subject slopes of $eGFRdiff_{cys-cr}$ were estimated from joint models of cystatin C-based estimated glomerular filtration rate (eGFRcys) and eGFRcr trajectory and survival, adjusted for baseline $eGFRdiff_{cys-cr}$

Subhazard ratios for incident HF hospitalization were obtained using Fine and Gray proportional subhazards regression, modeling mortality as a competing risk.