Title

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Journal

American Journal of Kidney Diseases, 76(6)

ISSN

0272-6386

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Publication Date

2020-12-01

DOI

10.1053/j.ajkd.2020.05.017

Peer reviewed

HHS Public Access

Author manuscript

Am J Kidney Dis. Author manuscript; available in PMC 2022 March 04.

Published in final edited form as:

Am J Kidney Dis. 2020 December ; 76(6): 765–774. doi:10.1053/j.ajkd.2020.05.017.

The Difference Between Cystatin C– and Creatinine-Based Estimated GFR and Associations With Frailty and Adverse Outcomes: A Cohort Analysis of the Systolic Blood Pressure Intervention Trial (SPRINT)

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Financial Disclosure: The authors declare that they have no relevant financial interests.

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Abstract

Rationale & Objective: In prior research and in practice, the difference between estimated glomerular filtration rate (eGFR) calculated from cystatin C level and eGFR calculated from creatinine level has not been assessed for clinical significance and relevance. We evaluated whether these differences contain important information about frailty.

Study Design: A cohort analysis of the Systolic Blood Pressure Intervention Trial (SPRINT).

Setting & Participants: 9,092 hypertensive SPRINT participants who had baseline measurements of serum creatinine, cystatin C, and frailty.

Exposure: eGFRs calculated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations ($eGFR_{cys}$ and $eGFR_{cr}$), and $eGFR_{Diff}$, calculated as $eGFR_{cys} - eGFR_{cr}$.

Outcomes: A validated 35-item frailty index that included questionnaire data for general and physical health, limitations of activities, pain, depression, sleep, energy level, self-care, and smoking status, as well as medical history, cognitive assessment, and laboratory data. We defined frailty as frailty index score > 0.21 (range, 0-1). The incidence of injurious falls, hospitalizations, cardiovascular events, and mortality was also recorded.

Analytical Approach: We used logistic regression to model the cross-sectional association of baseline $eGFR_{Diff}$ with frailty among all SPRINT participants. Adjusted proportional hazards regression was used to evaluate the association of $eGFR_{Diff}$ with adverse outcomes and mortality.

Results: Mean age was 68 ± 9 (SD) years, mean $eGFR_{cys}$ and $eGFR_{cr}$ were 73 ± 23 and 72 ± 20 mL/min/1.73 m^2, and mean $eGFR_{Diff}$ was 0.5 ± 15 mL/min/1.73 m^2. In adjusted models, each 1-SD higher $eGFR_{Diff}$ was associated with 24% lower odds of prevalent frailty (OR, 0.76; 95% CI, 0.71-0.81), as well as with lower incidence rate of injurious falls (HR, 0.84; 95% CI, 0.77-0.92), hospitalization (HR, 0.91; 95% CI, 0.88-0.95), cardiovascular events (HR, 0.89; 95% CI, 0.81-0.97), and all-cause mortality (HR, 0.71; 95% CI, 0.63-0.82); $P < 0.01$.

Limitations: Gold-standard measure of kidney function and assessment of muscle mass were not available.

Conclusions: The difference between $eGFR_{cys}$ and $eGFR_{cr}$ is associated with frailty and health status. Positive $eGFR_{Diff}$ is strongly associated with lower risks for longitudinal adverse outcomes and mortality, even after adjusting for chronic kidney disease stage and baseline frailty.

Kidney function is typically assessed by calculating an estimated glomerular filtration rate (eGFR) based on serum creatinine level ($eGFR_{cr}$), with $eGFR_{cr}$ > 60 mL/min/1.73 m^2 indicating normal kidney function. Although generally viewed as solely a kidney function marker, creatinine is a product of muscle metabolism that is filtered by the kidneys. Serum creatinine concentrations are known to be influenced by factors other than glomerular filtration,[1-3] in particular by muscle mass and diet. As a result, a high $eGFR_{cr}$ may reflect

low muscle mass. By contrast, serum cystatin C level offers an estimate of GFR ($eGFR_{cys}$) that is less dependent on muscle mass,[4] though it may be influenced by inflammation and levels appear to be higher in obese people. Cystatin C is a nonglycosylated protein produced at a constant rate by all nucleated cells rather than only muscle tissue and is freely filtered by glomeruli.[5]

Although substantial effort has gone into creating equations that incorporate both serum cystatin C and creatinine levels into 1 unified estimate of GFR ($_{eGFRcr\text{-}cys}$),[6,7] less attention has been paid to the clinical relevance of having different estimates of GFR[8] from cystatin C versus creatinine level. Although clinicians may be tempted to ignore these differences and combine the 2 estimates into 1 eGFR equation,[6] important clinical information may be lost by this practice. For example, it has been recognized that older age is associated with an increasing difference between GFR estimates.[9] Because muscle mass influences serum creatinine concentration more than cystatin C concentration, sarcopenia could in part be an explanation for the difference between these 2 measures. We hypothesized that large differences between these 2 GFR estimates may serve as a marker of health status and/or frailty, particularly in older adults, regardless of the “true” level of kidney function.

As the growing clinical use of $eGFR_{cys}$ in the ambulatory setting provides increasing opportunities for clinicians to evaluate both an $eGFR_{cys}$ and an $eGFR_{cr}$ in the same patient, it is important to understand the factors that associate with disparate eGFRs by these 2 markers. We hypothesized that the differences between eGFRs ($eGFR_{Diff}$) obtained using $eGFR_{cys}$ and $eGFR_{cr}$ would associate with prevalent frailty and with longitudinal outcomes related to aging, such as injurious falls, hospitalizations, cardiovascular events, and all-cause mortality. To investigate these hypotheses, we evaluated participants in the Systolic Blood Pressure Intervention Trial (SPRINT),[10] a randomized trial of 2 different blood pressure targets among a large sample of participants 50 years and older that oversampled persons older than 75 years.

Methods

Study Population

SPRINT enrolled 9,361 hypertensive adults and compared treatment with a systolic blood pressure target of <120 mm Hg (intensive treatment) versus a target of <140 mm Hg (standard treatment) on the incidence of cardiovascular morbidity and mortality. All-cause mortality was a prespecified secondary end point. The design and primary outcome results of the study have been previously described.[10,11] Participants were enrolled between November 2010 and March 2013. To be included, participants had to be at least 50 years old with systolic blood pressure ≥130 mm Hg, and (1) be at increased risk for cardiovascular disease (CVD), defined as having a 10-year Framingham Risk score ≥ 15% within the past 12 months; (2) have a history of clinical or subclinical CVD other than stroke, such as ischemic heart disease, peripheral arterial disease, or aortic aneurysm; or (3) be at least 75 years old. Exclusion criteria included a history of diabetes mellitus, polycystic kidney disease, stroke, or proteinuria of more than 1 gram per day, and eGFR < 20 mL/min/1.73 m^2 at baseline. This analysis also excluded 269 participants who did not have cystatin

C, creatinine, or measures of frailty at baseline, resulting in an analytic sample of 9,092 participants (97.1% of SPRINT).

Exposure

Samples for serum creatinine and cystatin C were collected at baseline. Serum creatinine was measured on a Roche Chemistry Analyzers (Roche Diagnostics Corp) using a creatinase enzymatic method with calibration traceable to an isotope-dilution mass spectrometry procedure. Cystatin C was measured using the Gentian assay (Gentian AS) at baseline. eGFRs were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C equation for $eGFR_{cys}$ and the CKD-EPI creatinine equation for $eGFR_{cr}$.[6] The variable of interest, $eGFR_{Diff}$, was calculated as $eGFR_{cys} - eGFR_{cr}$, meaning that positive values indicated a higher $eGFR_{cys}$ and negative numbers indicated a higher $eGFR_{cr}$. $eGFR_{cr\text{-}cys}$ was calculated using the CKD-EPI creatinine–cystatin C equation.

Clinical Outcomes

Frailty status was quantified at baseline using a previously developed frailty index, based on the model of deficit accumulation.[12] The original frailty index included 37 items derived from self-administered questionnaires (asking about general and physical health, limitations of activities, pain, depression, sleep, energy level, self-care, and smoking status), medical history (stroke, angina, heart attack, heart failure, atrial fibrillation, diabetes, and cancer), blood pressure measures, body mass index (BMI), laboratory data (including lipid and chemistry panels), neuropsychological testing of cognitive function (Montreal Cognitive Assessment, Logical Memory Delayed Recall, and the Digit Symbol Coding test), and gait speed (in participants ≥75 years). Given the focus of this analysis on measures of kidney function, we removed deficits based on eGFR and urinary albumin-creatinine ratio from the frailty index (reducing it to 35 items). The frailty index was calculated as the sum of the score for each deficit, divided by the total number of nonmissing items; each criterion was weighted equally, and participants with at least 30 nonmissing items were included.[12-14] The range of possible frailty index scores is thus 0 to 1 (inclusive), with those scoring 0 being the healthiest and those scoring 1 being the most frail (high proportion of functional deficits). Participants with a frailty index score > 0.21 were considered frail.[15] Frailty index score ≤ 0.10 classified participants as fit, and 0.10 < frailty index ≤ 0.21 as less fit. These cut-points were defined a priori and were chosen because they were used as the frailty indicator in a prior SPRINT article.[12] The frailty index was previously validated[13,16] and enables accurate risk-stratification for falls and all-cause hospitalizations. The frailty index score distribution within the SPRINT cohort was found to be comparable to that in the general population.[12]

Gait speed was measured only in the subset of participants 75 years and older (n = 2,513) in SPRINT. Participants were asked to walk 4 m, at their usual pace, twice. The average of the 2 measurements was used to define gait speed for analysis. The help of an assistive device was allowed if typically used by the participant. Participants were defined as “normal” walkers if gait speed was ≥0.8 m/s, a walking time ≤ 3.2 seconds, and as “slow” walkers if <0.8 m/s.[17]

Adverse events were assessed at follow-up visits at least quarterly during the trial, including myocardial infarction, stroke, acute coronary syndrome, heart failure, injurious falls, hospitalizations, and mortality. Reports of emergency department visits, procedures, and hospitalizations were obtained, and cardiovascular events were adjudicated centrally by prespecified criteria.

Other Study Measurements

Sociodemographic data, including age, sex, ethnicity, and level of education, were collected by self-administered questionnaires. Similarly, medical history, tobacco use, and medication lists were assessed using questionnaires. BMI was calculated based on baseline weight and height. Blood pressure was measured with an automated measurement system (Model 907; Omron Healthcare) 3 times 1 minute apart after 5 minutes of rest.[18] The mean of the 3 readings was used for analyses. Baseline measurements of cholesterol, serum albumin, and urinary albumin-creatinine ratio were used for analysis for this study.

Statistical Analysis

We initially considered our primary predictor variable $eGFR_{Diff}$ as a continuous variable. For descriptive purposes in companion analyses, the study population was then divided into 3 groups based on baseline $eGFR_{Diff}$ (in mL/min/1.73 m^2) as follows: negative ($eGFR_{Diff} < -15$), reference ($-15 \leq eGFR_{Diff} < +15$), and positive ($eGFR_{Diff} \geq +15$). eGFR equations are an approximation of kidney function and thus somewhat imprecise, so we thought it best to evaluate a range rather than a specific value. We opted for a cutoff of 15 mL/min/1.73 m^2 because it corresponds to 1 standard deviation (SD) and approximates the difference in eGFRs between chronic kidney disease (CKD) categories. We calculated participants' baseline characteristics across groups, using mean ± SD for continuous variables and number with percent for categorical variables.

For cross-sectional analyses at baseline, we used logistic regression to model the association of $eGFR_{Diff}$ with frailty and linear regression to assess its association with gait speed. We initially considered unadjusted models. For adjusted models, model 1 was adjusted for CKD stage by $eGFR_{cr}$; model 2, for CKD stage by $eGFR_{cr}$, sociodemographic characteristics (age, sex, and race), treatment group, urinary albumin-creatinine ratio, and cardiovascular risk factors (history of CVD, systolic blood pressure, number of baseline blood pressure medications, high-density lipoprotein cholesterol level, total cholesterol level, and smoking status). Both logistic and linear regression models incorporating $eGFR_{cr}$ as a continuous variable did not converge, likely due to collinearity with the predictor variable of interest ($eGFR_{Diff}$).

We used restricted cubic splines to look at the functional form of $eGFR_{Diff}$ with injurious falls, hospitalizations, cardiovascular events, and mortality. Knots were placed at the quartiles of the distributions of $eGFR_{Diff}$.

Proportional hazards regression was used to evaluate the association of $eGFR_{Diff}$ with each time-to-event outcome: injurious falls, hospitalizations, cardiovascular events, and mortality. Kaplan-Meier curves were created. We included covariates using the same set of nested models as described, with the exception that models 2 were also adjusted for frailty index.

Finally, to assess for an effect on our findings, we tested for interactions by treatment group, by age (<65 vs ≥65 years on the one hand and <75 vs ≥75 years on the other hand), by sex, by race, and by BMI on the association between $eGFR_{Diff}$ and each outcome. We also tested for an interaction by congestive heart failure on the association between $eGFR_{Diff}$ and cardiovascular events and mortality.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp) and R Core Team (2019), version 3.6.0 (R Foundation for Statistical Computing). The SPRINT protocol was approved by institutional review boards at each of the trial sites, including at Veterans Affairs San Diego, and all participants provided informed consent.

Results

Baseline Characteristics and Determinants of $eGFR_{Diff}$

The 9,092 participants' baseline characteristics are shown in Table 1. Average age was 68 ± 9 years and $eGFR_{cys}$ was 73 ± 23, $eGFR_{cr}$ was 72 ± 20, and $eGFR_{Diff}$ was 0.5 ± 15 mL/min/1.73 m^2. Compared with participants with minimal differences in eGFRs, those in the positive $eGFR_{Diff}$ group (≥15 mL/min/1.73 m^2) indicating higher $eGFR_{cys}$ than $eGFR_{cr}$, were younger, more likely to be male, and more likely to have a lower BMI. The distributions of $eGFR_{cys}$, $eGFR_{cr}$, and $eGFR_{Diff}$ in the SPRINT population are shown in Figure 1.

Association of $eGFR_{Diff}$ With Prevalent Frailty

When considering $eGFR_{Diff}$ as a continuous variable, each 1-SD higher $eGFR_{Diff}$ was associated with 24% lower prevalence of frailty in the fully adjusted model (Table 2). Similarly, when we divided the population into 3 groups based on $eGFR_{Diff}$, the relationship appeared largely monotonic. After multivariable adjustment, the negative-$eGFR_{Diff}$ group had 41% higher odds of being frail compared with the reference group, a statistically significant difference. Those in the positive-$eGFR_{Diff}$ group were 39% less likely to be frail (Table 2). When stratifying the population by categories of $eGFR_{cr}$ (<45, 45-60, 60-90, and ≥90 mL/min/1.73 m^2), $eGFR_{Diff}$ remained strongly and significantly associated with prevalent frailty in each stratum (Table S1).

Association of $eGFR_{Diff}$ With Walking Speed

Gait speed was measured among 2,513 participants 75 years and older at baseline. Among this subgroup, the average time to walk 4 m was approximately 6 seconds. Each 1-SD higher $eGFR_{Diff}$ was associated with an 8% faster walking time (β = −0.47 [95% CI, −0.93 to −0.02]; 8% faster walking time is calculated as this β divided by the average walking time of the sample, ie, 6 seconds).

Association of $eGFR_{Diff}$ With Incidence of Injurious Falls, Hospitalizations, CVD, and Mortality

Adjusted spline curves represent the relationships of the full range of $eGFR_{Diff}$ (Fig 2) with risks for injurious falls, hospitalizations, cardiovascular events, and mortality. Lower $eGFR_{Diff}$ was associated with higher risk for all outcomes (Fig S1).

In multivariable analyses, each 1-SD higher $eGFR_{Diff}$ at baseline was associated with 16% lower risk for injurious falls, 9% lower risk for hospitalizations, 11% lower risk for CVD events, and 29% lower risk for mortality (Table 3). These findings were all highly statistically significant across the series of models and remained statistically significant after adjustment for baseline frailty. Treatment did not modify the association of $eGFR_{Diff}$ with any of these outcomes (all P for interaction ≥ 0.49). Congestive heart failure did not modify the association with CVD or mortality (P for interaction = 0.09 and 0.07, respectively). We found little evidence of interaction by age on the association between $eGFR_{Diff}$ and risk for CVD or injurious falls. Sex modified the association between $eGFR_{Diff}$ and injurious falls (P = 0.03; Table 4).

Discussion

This study shows that the difference in calculated $eGFR_{cr}$ and $eGFR_{cys}$ provides clinical information about frailty status and risk for adverse events and suggests that using the combined CKD-EPI creatinine–cystatin C equation to estimate GFR may lead to the loss of important clinical information, although it may provide a more accurate estimation of GFR.[6] We were struck by the finding that nearly a third of the cohort (2,621/9,092 [29%]) had differences in $eGFR_{cr}$ and $eGFR_{cys}$ ≥ 15 mL/min/1.73 m^2. Consistent with our hypothesis, we showed that higher $eGFR_{Diff}$ (ie, higher $eGFR_{cys}$ than $eGFR_{cr}$) was strongly associated with lower odds of prevalent frailty independent of age, clinical markers, and stage of kidney disease. Further, higher $eGFR_{Diff}$ was associated with lower risk for important outcomes during follow-up, including incidence of injurious falls, hospitalizations, CVD events, and mortality. These associations were statistically very strong, independent of demographics and clinical factors at baseline, and appeared similar in both treatment groups in SPRINT. They complement recent findings from the Cardiovascular Health Study, where higher $eGFR_{Diff}$ was associated with lower risk of incident frailty and mortality.[19]

Unexpectedly, the association of $eGFR_{Diff}$ with injurious falls, hospitalizations, cardiovascular events, and mortality remained consistent even after adjusting for baseline frailty. This suggests that $eGFR_{Diff}$ contains information about the risk for these outcomes and notably about mortality risk independent of the frailty measure in SPRINT. It is possible that the frailty index used here does not capture all aspects of frailty. One potential explanation for the association between $eGFR_{Diff}$ and CVD could be through the known relationship[20,21] between kidney failure and CVD. We have adjusted the models for $eGFR_{cr}$ category, but this marker is also part of our exposure variable and unfortunately we could not account for true kidney function (measured GFR was not available). We found that the association between $eGFR_{Diff}$ and CVD and mortality was similar in groups with and without congestive heart failure.

Since creatinine and cystatin C levels are both influenced by body composition, it is possible that the association between $eGFR_{Diff}$ and frailty is related to sarcopenia. Although sarcopenia is a clinical diagnosis,[22] there are several ways to assess muscle mass with imaging, such as dual-energy x-ray absorptiometry, computed tomography, or magnetic resonance imaging. These tests are costly and entail radiation. Bioimpedance is an inexpensive alternative to assess body composition but is influenced by factors[23] such as hydration status, nutrition, and limb size. Instead, we propose a laboratory test that is readily available and time effective that may capture not only sarcopenia but frailty, which is a complex phenotype. The SPRINT frailty index was constructed a priori and includes 35 criteria (excluding albuminuria and eGFR), making it a comprehensive tool. Most of those can be assessed in the clinic (questionnaires, medical history, and laboratory results). We acknowledge the limitation to generalize our findings given the unique “nonclassic” marker of frailty used here. However, although it has not been used in other settings, the SPRINT frailty index has been validated[12,13,16] and its distribution was found to be similar to that of frailty in observational studies.

This study has several strengths. SPRINT enrolled a large population of hypertensive patients, with specific enrichment for those with CKD and for older patients. Participants were enrolled at various clinical sites across the United States, capturing variability in patient population and clinical approaches. Creatinine and cystatin C were measured in a central laboratory for all participants. Cardiovascular outcomes included myocardial infarction, stroke, acute coronary syndrome, and heart failure and were centrally adjudicated based on review of hospital records. Quality control procedures were applied, including percent agreement of individual study adjudicators with the final outcome assignments.

The study also has important limitations. Cystatin C may not yet be widely ordered and is more costly than creatinine, making its use limited. However, it is less expensive and devoid of side effects (such as radiation) compared to computed tomography or dual-energy x-ray absorptiometry and using it as part of an $eGFR_{Diff}$ may provide important information about frailty versus these more invasive tests. All participants were hypertensive and individuals with diabetes were excluded. Injurious falls were not further validated beyond self-report and may have been underestimated. We had neither measured GFR to use as a gold-standard comparator nor objective measures of muscle mass. Future research should examine whether $eGFR_{Diff}$ is associated with measures of muscle mass, as we hypothesize.

We considered whether those with a negative $eGFR_{Diff}$ may systematically have worse GFRs, and the association is therefore confounded by the known relationship between eGFR and frailty. However, the relationship between $eGFR_{Diff}$ and prevalent frailty remained strong and significant across categories of $eGFR_{cr}$. We also found that the association between $eGFR_{Diff}$ and adverse outcomes remained consistent in fully adjusted models. These findings add confidence that $eGFR_{Diff}$ embeds important clinical information independent of GFR. We acknowledge that it may not be financially feasible to measure cystatin C in everyone, but we believe it should then be targeted to people for whom there is a clinical suspicion of frailty. This would allow to better identify frail older adults and their prognosis. And in turn, it could contribute to improving goals of care communications and timing around dialysis access placement.

In summary, almost a third of the SPRINT population had differences in GFR estimates > 15 mL/min/1.73 m^2 when comparing eGFR from cystatin C with creatinine. Those with a positive $eGFR_{Diff}$ (≥15 mL/min/1.73 m^2) were less likely to be frail, as well as at lower risk for injurious falls, hospitalizations, cardiovascular events, and mortality. Clinical recognition of these differences will allow clinicians to obtain information embedded in these 2 tests, traditionally thought of as measuring only kidney function, on their patients' overall health status and prognosis for adverse outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Support:

Dr Potok was supported by grant 5T32DK104717, by the American Kidney Fund Clinical Scientist in Nephrology Fellow Program, and Akebia Therapeutics, Inc. Dr Rifkin was supported by K23 DK09152 and Veterans' Affairs Merit Award H160180 (Health Services Research and Development). Dr Pajewski was supported by the Wake Forest Claude Pepper Center (P30 AG021332). Cystatin C measurements were supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to Drs Ix and Shlipak (R01DK098234). Additional support was provided by grants K24DK110427 (Dr Ix), and the American Heart Association (grant 14EIA18560026 to Dr Ix). SPRINT is funded with federal funds from the National Institutes of Health (NIH), including the National Heart, Lung, and Blood Institute, the NIDDK, the National Institute on Aging, and the National Institute of Neurological Disorders and Stroke, under contract numbers HHSN268200900040C, HHSN 268200900046C, HHSN268200900047C, HHSN2682 00900048C, and HHSN268200900049C and Inter-Agency Agreement Number A-HL-13-002-001. It was also supported in part with resources and use of facilities through the Department of Veterans Affairs. The SPRINT investigators acknowledge the contribution of study medications (azilsartan and azilsartan combined with chlorthalidone) from Takeda Pharmaceuticals Int, Inc. All components of the SPRINT protocol were designed and implemented by the investigators, and the investigative team collected, analyzed, and interpreted the data. We also acknowledge support from the following Clinical and Translational Science Awards funded by National Center for Advancing Translational Sciences of the NIH (Case Western Reserve University: UL1TR000439; Ohio State University: UL1RR025755; University of Pennsylvania: UL1RR024134 and UL1TR000003; Boston University: UL1RR025771; Stanford University: UL1TR000093; Tufts University: UL1RR025752, UL1TR000073 and UL1TR001064; University of Illinois: UL1TR000050; University of Pittsburgh: UL1TR000005; University of Texas Southwestern: 9U54TR000017-06; University of Utah: UL1TR000105-05; Vanderbilt University: UL1TR000445; George Washington University: UL1TR000075; University of California, Davis: UL1TR000002; University of Florida: UL1TR000064; University of Michigan: UL1TR000433; and Tulane University: P30GM103337 COBRE Award NIGMS). The funders did not have a role in study design; collection, analysis, or interpretation of the data; or writing of the manuscript.

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PLAIN-LANGUAGE SUMMARY

The difference between cystatin C– and creatinine-based estimated glomerular filtration rates (eGFRs) contains important clinical information. It is common to see clinic patients whose eGFRs using creatinine and cystatin C levels differ by >15 mL/min/1.73 m^2. We surmised that these differences, usually overlooked in favor of a combined eGFR, carry important information beyond their use as GFR estimates. We examined the intraindividual difference in eGFRs using cystatin C versus creatinine level ($eGFR_{Diff}$) and found that $eGFR_{Diff}$ may hold prognostic information: a negative $eGFR_{Diff}$ at any level of kidney function was associated with higher risk for frailty, cardiovascular disease, and death. We speculate that this may be due to non–GFR-related creatinine and cystatin C correlates and suggest that $eGFR_{Diff}$ may represent a tool to improve our ability to identify individuals at high risk for these outcomes.

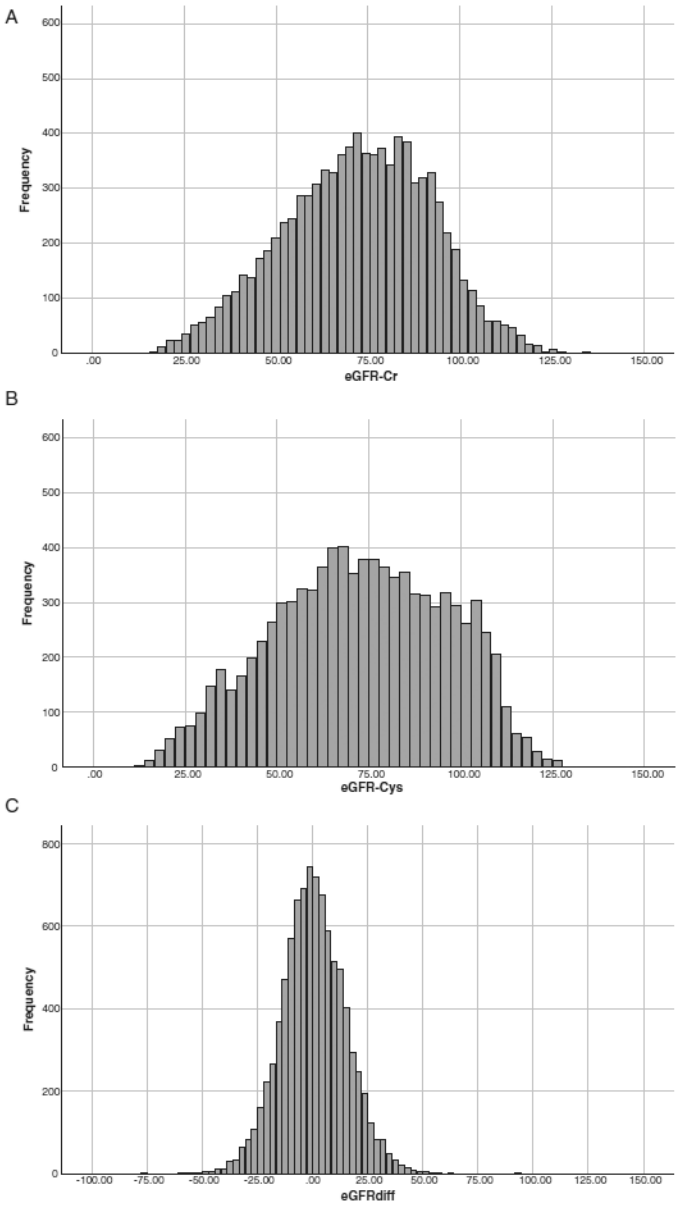

Figure 1.

Distributions of glomerular filtration rate (GFR) estimated using serum cystatin C level ($eGFR_{cys}$), GFR estimated using creatinine level ($eGFR_{cr}$), and $eGFR_{Diff}$ ($eGFR_{cys} - eGFR_{cr}$).

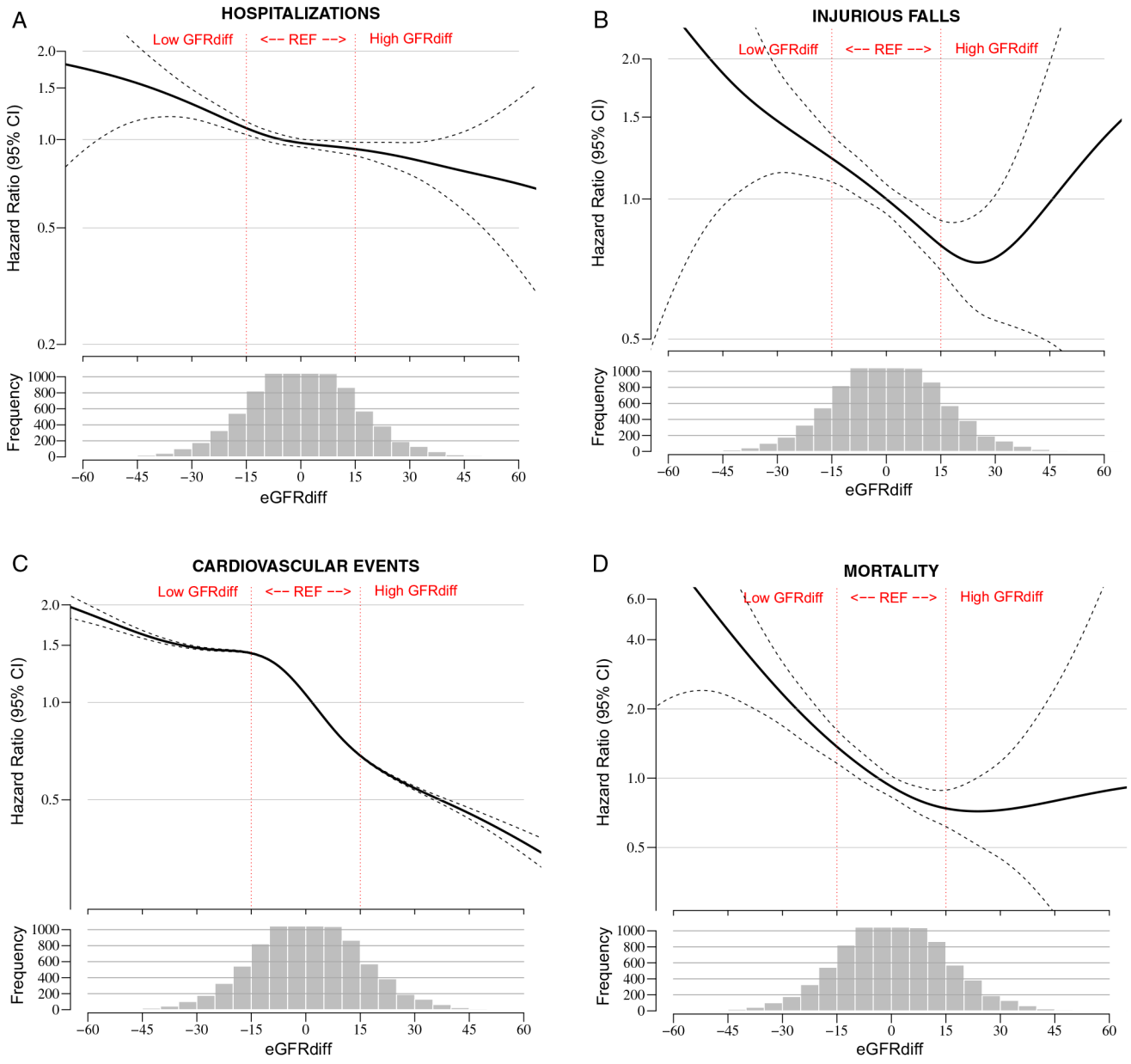

Figure 2.

Adjusted spline curves of the association of the difference in estimated glomerular filtration rate ($eGFR_{Diff}$; GFR estimated using cystatin C level [$eGFR_{cys}$] – GFR estimated using creatinine level [$eGFR_{cr}$]) with injurious falls, hospitalizations, cardiovascular events, and mortality. Abbreviations: CI, confidence interval; REF, reference.

Am J Kidney Dis. Author manuscript; available in PMC 2022 March 04.

Table 1.

Baseline Characteristics of SPRINT Participants by $eGFR_{Diff}$ ($eGFR_{cys} - eGFR_{cr}$)

	$eGFR_{Diff}$ Group			
	Negative (<−15)	**Reference (−15 to +15)**	**Positive (≥15)**	**total**
Sample size	1,230 (14%)	6,471 (71%)	1,391 (15%)	9,092 (100%)
Age, y	68 ± 10	69 ± 9	65 ± 8	68 ± 9
Male sex	665 (54%)	4,127 (64%)	1,050 (76%)	5,842 (64%)
Race				
White	642 (52%)	3,890 (60%)	727 (52%)	5,259 (58%)
Black	440 (36%)	1,805 (28%)	454 (33%)	2,699 (30%)
Other	148 (12%)	776 (12%)	210 (15%)	1,134 (13%)
Education level				
<HS	145 (12%)	622 (10%)	88 (6%)	855 (9%)
HS diploma/vocational/some college	631 (51%)	2,886 (45%)	553 (40%)	4,070 (45%)
≥College graduate	454 (37%)	2,962 (46%)	750 (54%)	4,166 (46%)
Smoking status				
Current	476 (39%)	2,860 (44%)	687 (50%)	4,023 (44%)
Former	472 (38%)	2,816 (44%)	575 (41 %)	3,863 (43%)
Never	282 (23%)	787 (12%)	127 (9%)	1,196 (13%)
BMI, kg/m^2	32.0 ± 7.4	29.7 ± 5.5	28.7 ± 4.7	29.8 ± 5.8
Height, in	66.3 ± 4.2	66.8 ± 4.0	67.8 ± 3.8	66.9 ± 4.0
Weight, lb	200 ± 50	189 ± 40	188 ± 37	190 ± 41
Prevalent CVD	269 (22%)	1,329 (21%)	220 (16%)	1,818 (20%)
Systolic BP, mm Hg	140 ± 16	140 ± 16	139 ± 15	140 ± 16
Diastolic BP, mm Hg	78 ± 12	78 ± 12	80 ± 11	78 ± 12
Total cholesterol, mg/dL	187 ± 43	190 ± 41	195 ± 40	190 ± 41
HDL cholesterol, mg/dL	51 ± 15	53 ± 14	55 ± 15	53 ± 14
$eGFR_{cys}$, mL/min/1.73 m^2	59 ± 17	70 ± 23	95 ± 15	73 ± 23
$eGFR_{cr}$, mL/min/1.73 m^2	82 ± 18	71 ± 21	72 ± 14	72 ± 20

	$eGFR_{Diff}$ Group			
	Negative (<−15)	**Reference (−15 to +15)**	**Positive (≥15)**	**total**
$eGFR_{cr\text{-}cys}$, mL/min/1.73 m^2	69 ± 18	71 ± 22	84 ± 15	73 ± 21
$eGFR_{Diff}$, mL/min/1.73 m^2	23 ± 7	0 ± 8	23 ± 8	0.5 ± 15
UACR, mg/g	11 [7-29]	10 [6-22]	7 [5-14]	10 [6-21]
Frail at baseline	379 (31%)	1,573 (24%)	173 (13%)	2,125 (23%)
4 m walking time, s[a]	6.5 ± 9.1	6.1 ± 9.3	5.3 ± 6.1	6.0 ± 9.0

Note: Values for continuous variables given as mean ± standard deviation or median [interquartile range]; values for categorical variables given as count (percent). All $P < 0.001$ except for 4-m walking time, $P = 0.3$, and systolic blood pressure, $P = 0.08$.

Abbreviations and definitions: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2); $eGFR_{cr}$, glomerular filtration rate estimated using serum creatinine level; $eGFR_{cys}$, glomerular filtration rate estimated using cystatin C level; $eGFR_{Diff}$, $eGFR_{cys}$ – $eGFR_{cr}$; HDL, high-density lipoprotein; HS, high school; SPRINT, Systolic Blood Pressure Intervention Trial; UACR, urinary albumin-creatine ratio.

[a]Participants with gait speed: total n = 2,513 (n = 354, 1,946, and 213 in negative, reference, and positive $eGFR_{Diff}$ groups, respectively).

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Table 2.

Association of $eGFR_{Diff}$ With Frailty at Baseline

		$eGFR_{Diff}$ Group		
	$eGFR_{Diff}$ (per 1-SD greater)	**Negative (<−15)**	**Reference (−15 to +15)**	**Positive (≥15)**
Sample size	2,125	379	1,573	173
OR (95% CI)				
Unadjusted	0.75 (0.71-0.79)	1.28 (1.11-1.46)	1.00 (reference)	0.50 (0.42-0.60)
Adjusted for $eGFR_{cr}$ CKD stage	0.72 (0.68-0.76)	1.63 (1.41-1.89)	1.00 (reference)	0.59 (0.49-0.70)
Fully adjusted[a]	0.76 (0.71-0.81)	1.41 (1.21-1.65)	1.00 (reference)	0.61 (0.50-0.73)

Note: Frailty defined as frailty index score > 0.21.

Abbreviations and definitions: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; $eGFR_{cr}$, glomerular filtration rate estimated using serum creatinine level; $eGFR_{cys}$, glomerular filtration rate estimated using cystatin C level; $eGFR_{Diff}$, $eGFR_{cys}$ – $eGFR_{cr}$ (in mL/min/1.73 m^2); OR, odds ratio; SD, standard deviation (here, 15 mL/min/1.73 m^2).

[a]Adjusted for age, sex, race, randomization arm, urinary albumin-creatinine ratio, history of cardiovascular disease, systolic blood pressure, number of baseline blood pressure medications, high-density lipoprotein cholesterol level, total cholesterol level, smoking status, and $eGFR_{cr}$ CKD stage.

Table 3.

Association of $eGFR_{Diff}$ With Risk for Injurious Falls, Hospitalizations, Cardiovascular Events, and Mortality

Parameter	Value
Injurious Falls	
No. of events	711
Annual incidence rate	2.5%
HR (95% CI) per 1 SD greater $eGFR_{Diff}$	
Unadjusted	0.77 (0.71-0.83)
Adjusted for $eGFR_{cr}$ CKD stage	0.72 (0.67-0.78)
Fully adjusted[a]	0.84 (0.77-0.92)
Hospitalizations	
No. of events	3,573
Annual incidence rate	15.07%
HR (95% CI) per 1 SD greater $eGFR_{Diff}$	
Unadjusted	0.83 (0.80-0.86)
Adjusted for $eGFR_{cr}$ CKD stage	0.81 (0.78-0.84)
Fully adjusted[a]	0.91 (0.88-0.95)
CVD Events	
No. of events	707
Annual incidence rate	2.11%
HR (95% CI) per 1 SD greater $eGFR_{Diff}$	
Unadjusted	0.76 (0.71-0.82)
Adjusted for $eGFR_{cr}$ CKD stage	0.72 (0.66-0.78)
Fully adjusted[a]	0.89 (0.81-0.97)
Total Mortality	
No. of events	354
Annual incidence rate	1.22%
HR (95% CI) per 1 SD greater $eGFR_{Diff}$	
Unadjusted	0.66 (0.60-0.74)
Adjusted for $eGFR_{cr}$ CKD stage	0.60 (0.53-0.67)
Fully adjusted[a]	0.71 (0.63-0.82)

Note: Interaction by treatment group: all $P > 0.5$; interaction by race: all $P > 0.1$; interaction by body mass index: all $P > 0.2$.

Abbreviations and definitions: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; $eGFR_{cr}$, glomerular filtration rate estimated using serum creatinine level; $eGFR_{cys}$, glomerular filtration rate estimated using cystatin C level; $eGFR_{Diff}$, $eGFR_{cys} - eGFR_{cr}$ (in mL/min/1.73 m^2); HR, hazard ratio; SD, standard deviation (here, 15 mL/min/1.73 m^2).

[a]Adjusted for age, sex, race, randomization arm, urinary albumin-creatinine ratio, history of CVD, systolic blood pressure, number of baseline blood pressure medications, high-density lipoprotein cholesterol level, total cholesterol level, smoking status, and $eGFR_{cr}$ CKD stage.

Table 4.

Association of $eGFR_{Diff}$ Groups With Injurious Falls Stratified by Age and Sex and CVD Events Stratified by Age

	$eGFR_{Diff}$ Group		
	Negative (<−15)	**Reference (−15 to +15)**	**Positive (≥15)**
Injurious Falls (*P* interaction= 0.02)			
Age < 65 y			
HR (95% CI)	1.89 (1.28-2.79)	1.00 (reference)	0.88 (0.55-1.39)
No. of patients	568	2,703	837
No. of events	42	110	28
Age ≥ 65 y			
HR (95% CI)	1.29 (1.01-1.65)	1.00 (reference)	0.44 (0.29-0.66)
No. of patients	662	3,768	554
No. of events	91	411	29
Injurious Falls (*P* interaction= 0.03)			
Female sex			
HR (95% CI)	1.31 (0.97-1.77)	1.00 (reference)	1.00 (0.66-1.51)
No. of patients	565	2,344	341
No. of events	63	229	30
Male sex			
HR (95% CI)	1.38 (1.04-1.84)	1.00 (reference)	0.46 (0.30-0.72)
No. of patients	665	4,127	1,050
No. of events	70	292	27
CVD Events (*P* interaction= 0.001)			
Age < 75 y			
HR (95% CI)	1.66 (1.28-2.16)	1.00 (reference)	1.27 (0.94-1.70)
No. of patients	901	4,705	1,203
No. of events	85	62	261
Age ≥ 75 y			
HR (95% CI)	1.04 (0.7-1.44)	1.00 (reference)	0.43 (0.21-0.87)

	$eGFR_{Diff}$ Group		
	Negative (<−15)	**Reference (−15 to +15)**	**Positive (≥15)**
No. of patients	329	1,766	188
No. of events	47	243	9

Note: This table is based on the significant interaction terms from Table 3. HR adjusted for age, sex, race, randomization arm, urinary albumin-creatinine ratio, history of CVD, systolic blood pressure, number of baseline blood pressure medications, high-density lipoprotein cholesterol level, total cholesterol level, smoking, frailty index score, and chronic kidney disease stages by $eGFR_{Cr}$.

Abbreviations and definitions: CI, confidence interval; CVD, cardiovascular disease; eGFR: estimated glomerular filtration rate; $eGFR_{Cr}$, glomerular filtration rate estimated using serum creatinine level; $eGFR_{Cys}$, glomerular filtration rate estimated using cystatin C level; $eGFR_{Diff}$, $eGFR_{Cys} - eGFR_{Cr}$ (in mL/min/1.73 m^2); HR, hazard ratio.