Discordances between creatinine- and cystatin C-based estimated GFR and adverse clinical outcomes in routine clinical practice

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Discordances Between Creatinine- and Cystatin C–Based Estimated GFR and Adverse Clinical Outcomes in Routine Clinical Practice

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Rationale & Objective: Cystatin C is recommended for measuring estimated glomerular filtration rate (eGFR) when estimates based on creatinine ($eGFR_{cr}$) are not thought to be accurate enough for clinical decision making. While global adoption is slow, routine cystatin C testing in Sweden has been available for over a decade, providing real-world evidence about the magnitude of differences between $eGFR_{cys}$ and $eGFR_{cr}$ and their association with clinical outcomes.

Study Design: Observational study.

Setting & Participants: 158,601 adults (48% women; mean age 62 years, $eGFR_{cr}$ 80, and $eGFR_{cys}$ 73 mL/min/1.73/m^2) undergoing testing for creatinine and cystatin C on the same day in connection with a health care encounter during 2010-2018 in Stockholm, Sweden.

Exposure: Percentage difference of $eGFR_{cys}$ minus $eGFR_{cr}$ ($eGFR_{diff}$).

Outcome: Kidney failure with replacement therapy (KFRT), acute kidney injury (AKI), atherosclerotic cardiovascular disease (ASCVD), heart failure, and death.

Analytical Approach: Multivariable Cox proportional hazards regression.

Results: Discordances between $eGFR_{cr}$ and $eGFR_{cys}$ were common, with $eGFR_{cys}$ being lower than $eGFR_{cr}$ (negative $eGFR_{diff}$) in most cases (65%). Patients with larger negative $eGFR_{diff}$ were older, more often female, with higher $eGFR_{cr}$ and albuminuria, and more comorbid conditions. Compared with patients with similar $eGFR_{cys}$ and $eGFR_{cr}$, the lowest quartile ($eGFR_{cys}$ > 27% lower than $eGFR_{cr}$) had the higher HR of all study outcomes: AKI, 2.6 (95% CI, 2.4-2.9); KFRT, 1.4 (95% CI, 1.2-1.6); ASCVD, 1.4 (95% CI, 1.3-1.5); heart failure, 2.0 (95% CI, 1.9-2.2); and all-cause death, 2.6 (95% CI, 2.5-2.7). Conversely, patients in the highest quartile (positive $eGFR_{diff}$) were at lower risk.

Limitations: Observational study, lack of information on indications for cystatin C testing.

Conclusions: Cystatin C testing in routine care shows that many patients have a lower $eGFR_{cys}$ than $eGFR_{cr}$, and these patients have a higher risk of multiple adverse outcomes.

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Glomerular filtration rate (GFR) measurement is central to the practice of medicine, particularly to the identification, staging, and management of chronic kidney disease (CKD). Because measuring GFR requires specialized facilities to perform clearance measurements, serum concentrations of endogenous filtration markers are used in routine clinical practice to estimate GFR (eGFR). Creatinine is the most commonly used filtration marker, and guidance from the Kidney Disease: Improving Global Outcomes (KDIGO) workgroup in 2012 recommended additionally measuring cystatin C for confirmatory testing and in situations when creatinine is not accurate enough for clinical decision making.[1] While creatinine is related to age, sex, and muscle mass, cystatin C can be falsely elevated in other settings, such as chronic inflammation, obesity, smoking, and hyperthyroidism.[2-5] For these reasons, GFR estimated with both creatinine and cystatin C is generally accepted as a more accurate marker of measured GFR than either marker alone.[1,6] Despite the 2012 KDIGO recommendation, global adoption of cystatin C testing has been low, potentially affected by lack of access, higher costs than serum creatinine, and lack of clinical experience. In 2021, the US National Kidney Foundation (NKF) and American Society of Nephrology (ASN) reiterated the need for "efforts to facilitate increased, routine, and timely use of cystatin C," and many health care systems are now heeding this recommendation.[6]

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Cystatin C–based eGFR ($eGFR_{cys}$) and creatinine-based eGFR ($eGFR_{cr}$) measured in the same individual may be different, hereby defined as $eGFR_{diff}$, reflecting differences in non-GFR factors affecting their serum concentrations.[7] Whether a large $eGFR_{diff}$ in routine clinical practice is common and what such differences might signify in terms of clinical outcomes is not well known. Prior studies have primarily explored $eGFR_{diff}$ in research cohorts, clinical trials, and inpatient settings,[8-17] but these results may not be generalizable to the heterogeneous general population seeking health care.

In Sweden, routine testing of cystatin C has been longstanding practice owing to the pioneering work of Swedish researcher Anders Grubb and colleagues, who identified cystatin C as a filtration marker in 1985,[18] and to subsequent national implementation efforts.[19] Using the

PLAIN-LANGUAGE SUMMARY

Clinicians require guidance when there are discrepancies between the estimated glomerular filtration rate based on creatinine ($eGFR_{cr}$) and based on cystatin C ($eGFR_{cys}$) in the same individual. Routine cystatin C testing in Sweden for over a decade permits exploration of how common and large these discrepancies are, and their associations with adverse clinical outcomes. In this observational study, we found that discordances between $eGFR_{cys}$ and $eGFR_{cr}$ are common, and 1 in 4 patients tested had an $eGFR_{cys}$ > 28% lower than their $eGFR_{cr}$. We also show that an $eGFR_{cys}$ that is lower than the $eGFR_{cr}$ consistently identifies patients at higher risk of adverse outcomes, including cardiovascular events, kidney replacement therapy, acute kidney injury, and death.

population followed for outpatient care in the region of Stockholm, Sweden, we provide real-world evidence on the distribution of $eGFR_{diff}$ and whether any degree of $eGFR_{diff}$ is associated with risks of kidney failure with replacement therapy (KFRT), acute kidney injury (AKI), atherosclerotic cardiovascular disease (ASCVD), heart failure, or death.

Methods

Study Design and Setting

We used data from the Stockholm Creatinine Measurements (SCREAM) project, a health care utilization cohort from the region of Stockholm, Sweden, which has data from 2006 to 2019.[20] A single health care provider in the Stockholm region provides universal and tax-funded health care to 20%-25% of the population of Sweden. Using unique personal identification numbers, SCREAM linked regional and national administrative databases that hold complete information on demographics, health care utilization, laboratory tests undertaken, dispensed drugs, diagnoses, and vital status until the end of 2019 without loss of follow-up. The regional ethical review board in Stockholm approved the study (reference 2017/793-31); informed consent was not deemed necessary because all data were deidentified at the Swedish Board of Health and Welfare.

Study Population

We included all outpatient cystatin C measurements that occurred in Stockholm health care between January 1, 2010, and December 31, 2018, and that were accompanied by a creatinine measurement on the same day. We excluded measurements before 2010 because they were performed using nonstandardized methods. We also excluded measurements performed in patients younger than 18 years old and after KFRT initiation, as well as extreme $eGFR_{diff}$ values, defined as those outside the 0.1th to 99.9th percentiles of distribution, which may reflect laboratory measurement errors. When multiple observations per patient were available, we considered the first observation per patient as the index date of our study.

There is no particular algorithm or subset of patients in whom cystatin C testing is indicated in Stockholm's regional health care protocols. In its online manual, our central laboratory department only discusses the utility of cystatin C for a more accurate estimation of kidney function. Cystatin C is automatically included in the laboratory package for kidney function assessment together with creatinine and albuminuria. When ordered, the laboratory automatically reports $eGFR_{cys}$ together with $eGFR_{cr}$ and the average between these 2 measurements.

Study Exposure

The primary study exposure was the percentage difference between $eGFR_{cys}$ and $eGFR_{cr}$ ($eGFR_{diff}$), defined as $(eGFR_{cys} - eGFR_{cr})/eGFR_{cr}$, which is mathematically equivalent to the ratio of $eGFR_{cys}/eGFR_{cr}$ that has been evaluated in prior studies.[21] We also evaluated the absolute $eGFR_{diff}$ (in mL/min/1.73 m^2), defined as $eGFR_{cys} - eGFR_{cr}$. Both were parameterized into quartiles. Both $eGFR_{cr}$ and $eGFR_{cys}$ were calculated with the 2021 and 2012 CKD-EPI equations, respectively.[22,23] Plasma/serum creatinine and cystatin C were measured automatically at the 3 central laboratories that provide services to the region. These laboratories are frequently audited to ensure reproducibility and comparison across the region's unified health care by Equalis (Uppsala, Sweden, www.equalis.se/en). Although methods or analyzers have changed over the years, the creatinine methods have been IDMS traceable, and the cystatin C methods have been traceable to IFCC reference materials.[24,25]

Study Covariates

Study covariates at the index date included age, sex, comorbidities, ongoing medications, and albuminuria (definitions detailed in Table S1). We identified comorbidities through issued clinical diagnoses. We ascertained medications through registered pharmacy fills using the nationwide Prescribed Drug Registry, considering the medication to be concomitant if a pharmacy fill occurred within 6 months before the index date. We classified the severity of GFR reduction using KDIGO G categories based on index $eGFR_{cr}$.[26] We used urinary albumin-creatinine ratio (UACR) tests to define albuminuria status, using outpatient measurements performed within 1 year of the index date and log transformation to correct the right-skewed distribution. When UACR was not available, we approximated the urine protein-creatinine ratio (UPCR) or dipstick protein to UACR concentrations using the equations by Sumida et al.[27] When none of the urine measurements was available, a missing indicator was used, centering at an UACR of 10 mg/g in regression analyses.

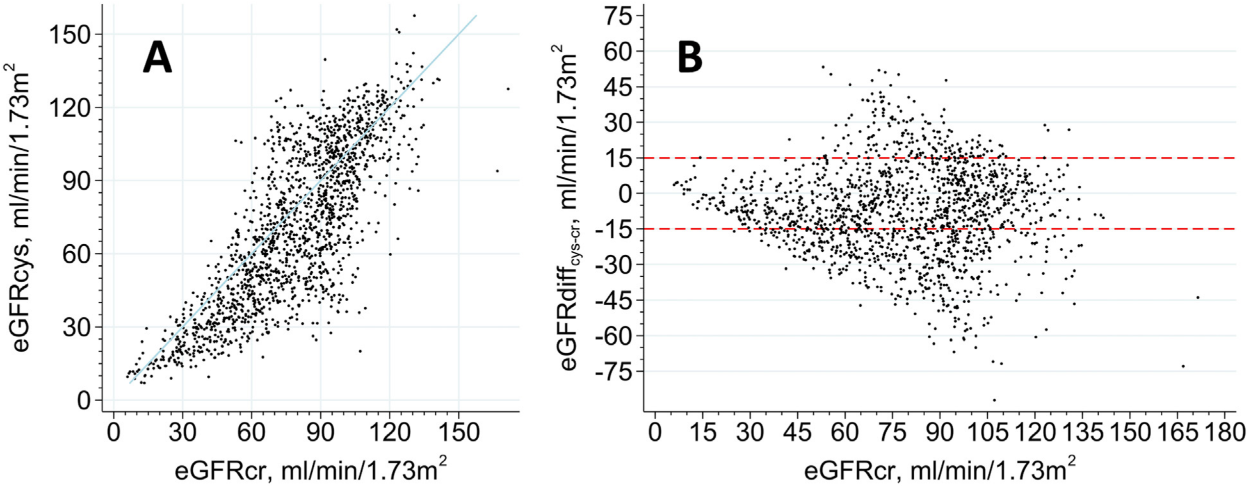

Figure 1. (A) Univariate correlation between $eGFR_{cys}$ and $eGFR_{cr}$, and (B) scatterplot of $eGFR_{cr}$ versus $eGFR_{diff}$ at baseline. Shown are correlations in a random 1% sample of 1,569 observations. The blue line shows the line of identity, and red line marks $eGFR_{diff}$ higher and lower than 15 mL/min/1.73 m². Abbreviations: cr, creatinine; cys, cystatin C; eGFR, estimated glomerular filtration rate.

Study Outcomes

We explored the association between index $eGFR_{diff}$ and the outcomes KFRT, AKI, heart failure, ASCVD, all-cause death, and cardiovascular death (definitions detailed in Table S1). KFRT was defined as a composite of maintenance dialysis or kidney transplantation. ASCVD was defined as a composite of myocardial infarction and stroke. Patients were followed from index date to the first occurrence of a study outcome, death, or end of the follow-up period (December 31, 2019), whichever occurred first.

Statistical Analyses

Descriptive tables and prospective analyses used quartile of $eGFR_{diff}$ based on the index measurement. We calculated the participants' baseline characteristics across quartiles, using mean ± SD for continuous variables and number with percent for categorical variables. We show both percent $eGFR_{diff}$ and absolute $eGFR_{diff}$.

The distribution of $eGFR_{diff}$ was described using kernel density plots. Scatterplots graphically depicted associations in a random 1% of the sample. Multinomial logistic regression was used to estimate the risk relationship between quartiles of $eGFR_{diff}$, selecting quartile 3 (similar $eGFR_{cr}$ and $eGFR_{cys}$) as the reference category, and participant characteristics as well as concomitant medications.

We calculated incidence rates with 95% confidence intervals and used multivariable-adjusted Cox proportional hazards regression for all-cause mortality and cause-specific hazards regression for other outcomes in the presence of competing events to study the association between quartiles of $eGFR_{diff}$ and time to outcomes. We adjusted for age, sex, hypertension, diabetes, history of CVD, baseline $eGFR_{cr}$ (modeled as splines with knots at 60 and 90 mL/min/1.73 m^2), and log-transformed UACR. We included $eGFR_{cr}$ in the adjustment variables because it is the most common measure of GFR assessed in clinical practice. To evaluate the continuous relationship between $eGFR_{diff}$ and outcomes, multivariable-adjusted Cox regression and piece-wise cubic splines of $eGFR_{diff}$ (knots at 25%, 50%, and 75%) were used to estimate associations with study outcomes.

We explored whether associations between $eGFR_{diff}$ and outcomes differed by baseline characteristics through stratified analyses. The a priori selected subgroups included age (< vs ≥ 65 years), female or male sex, KDIGO G categories by $eGFR_{cr}$, and presence/absence of hypertension, diabetes, or cardiovascular disease. All analyses were conducted using Stata MP version 16 (Stata Corp).

Results

Patient Selection and Descriptives

During 2010-2018, there were 452,992 outpatient cystatin C determinations taken in 172,044 unique individuals attending Stockholm health care with an outpatient serum creatinine measured on the same day (Fig S1). After excluding the measurements performed after KFRT, in patients with age < 18 years, and with extreme $eGFR_{diff}$ values, the study population consisted of 158,601 unique individuals.

The eGFRs reported by $eGFR_{cr}$ and $eGFR_{cys}$ were often dissimilar, with Figure 1A showing a considerable discordance. The $eGFR_{cys}$ measurement was generally lower than the $eGFR_{cr}$ (Fig 2A), and the majority of determinations (65%) disclosed a negative $eGFR_{diff}$, with mean −10% (± 25 SD) lower or mean −7 (± 19 SD) mL/min/1.73 m^2 lower (Fig 2B and C). We found that 32% of determinations had a negative $eGFR_{diff}$ of more than 15 mL/min/1.73 m^2. Discordances between $eGFR_{cys}$ and

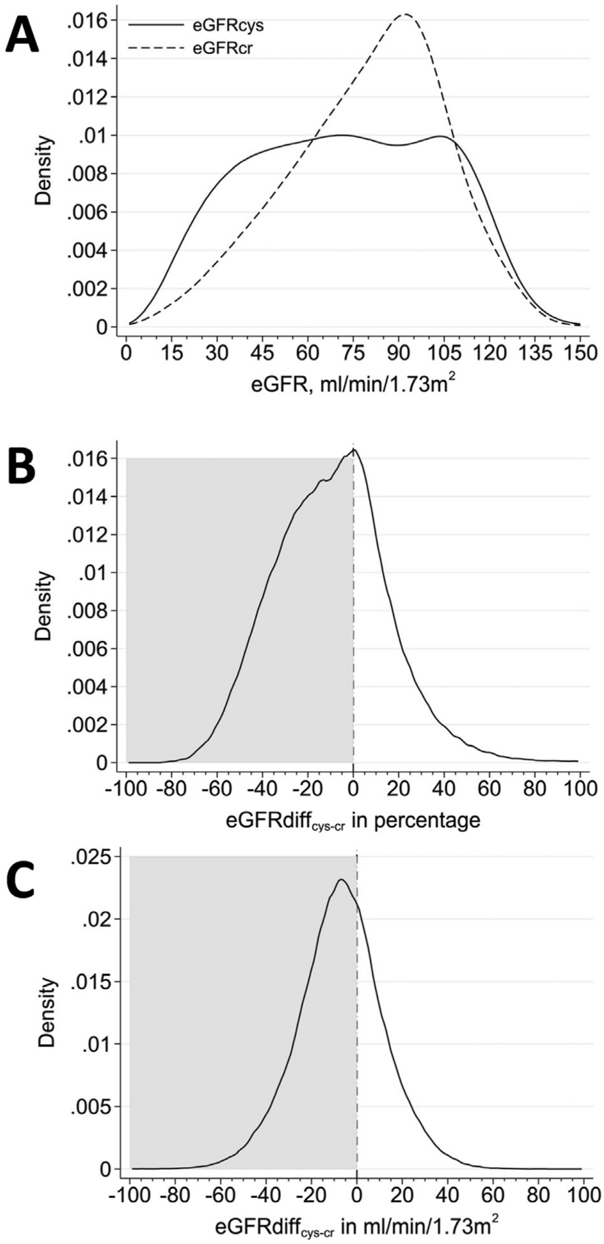

Figure 2. Kernel-density estimates showing the smoothed frequency for (A) 1 unit of $eGFR_{cr}$ and $eGFR_{cys}$, (B) percent $eGFR_{diff}$, and (C) absolute $eGFR_{diff}$. Distributions based on 158,663 paired determinations of creatinine/cystatin C. Shaded areas depict negative $eGFR_{diff}$ (ie, frequencies in which $eGFR_{cys}$ is lower than $eGFR_{cr}$). Abbreviations: cr, creatinine; cys, cystatin C; eGFR, estimated glomerular filtration rate.

$eGFR_{cr}$ were smallest among those with lower $eGFR_{cr}$ and widened at higher $eGFR_{cr}$ values (Fig 1B).

The baseline characteristics of the study participants are described in Table 1. Their mean age was 62 years (± 18 SD), and 48% were women. The mean $eGFR_{cys}$ was 73 mL/min/1.73 m^2, and mean $eGFR_{cr}$ was 80 mL/min/1.73 m^2. Table 1 also shows the baseline characteristics according to quartiles of percent $eGFR_{diff}$ distribution. Complementary descriptives for absolute $eGFR_{diff}$ are shown in Table S2. While participants within quartile 4 experienced a positive $eGFR_{diff}$ ($eGFR_{cys} > eGFR_{cr}$ by 6% or more), those within quartile 3 had minimal or no change between both eGFR estimates ($eGFR_{diff}$ between 9% lower and 5% higher); participants in the second and first quartiles, however, experienced a negative $eGFR_{diff}$ ($eGFR_{cys} < eGFR_{cr}$ by 10%-27% in quartile 2, and by >27% in quartile 1). In logistic regression (Tables S3 and S4) and compared with participants in quartile 3, those with negative $eGFR_{diff}$ (quartiles 1 and 2) were more likely to be older, were more often women, and had the highest prevalence of baseline comorbidities, including diagnosed hypertension, diabetes, cardiovascular disease, and cancer. They were also more likely to have a higher $eGFR_{cr}$ and higher UACR. The relationship of baseline percent and absolute $eGFR_{diff}$ is shown in Figure S2.

Association Between $eGFR_{diff}$ and Study Outcomes

During median 4.5 (IQR, 2.3-6.8) years of follow-up, we observed 36,587 deaths (10,442 attributed to cardiovascular diseases), and 7,625 ASCVD, 10,159 heart failure, 5,648 AKI, and 1,709 KFRT events (Table 2). Compared with the participants in quartile 3 (ie, minimal $eGFR_{diff}$), the participants within the negative $eGFR_{diff}$ categories (quartiles 1 and 2) had a higher risk of all study outcomes. Participants within the positive $eGFR_{diff}$ category (quartile 4) had a lower risk of all study outcomes (Fig 3; Table 2). The results from all subgroups are presented in Tables S5-S11.

Discussion

GFR is used in risk stratification and clinical decision making, but there is no guidance for when $eGFR_{cys}$ and $eGFR_{cr}$ are substantially different. This large observational study of patients undergoing cystatin C testing in the region of Stockholm showed that discordances between $eGFR_{cys}$ and $eGFR_{cr}$ are common, with 1 in 4 patients tested having an $eGFR_{cys}$ > 27% lower than their $eGFR_{cr}$. We also show that an $eGFR_{cys}$ that is lower than the $eGFR_{cr}$ consistently identifies patients at higher risk of adverse outcomes. The strengths of our study include its large sample size (more than 15-fold larger than previous studies) and unique setting that involves real-world patients from a country with long-standing cystatin C testing and universal tax-funded health care, which minimizes selection bias from disparate access to health care.

We observed large negative $eGFR_{diff}$, with a mean difference of −8 ± 19 (SD) mL/min/1.73 m^2. Most of the observations (65%) in our study had $eGFR_{cys}$ lower than the $eGFR_{cr}$, with 32% exhibiting differences larger than 15 mL/min/1.73 m^2. This contrasts with the smaller discordances often found in research cohorts or clinical trials[8-12]: for instance, in the Chronic Renal Insufficiency Cohort (CRIC) Study (n = 4,956),[10] the mean $eGFR_{diff}$ was +6 ± 16 (SD) mL/min/1.73 m^2; in the Systolic Blood

Table 1. Baseline Characteristics by Quartiles of Percent $eGFR_{diff}$

		Quartiles of $eGFR_{diff}$			
	Overall	Quartile 1 $eGFR_{cys}$ << $eGFR_{cr}$	Quartile 2 $eGFR_{cys}$ < $eGFR_{cr}$	Quartile 3 $eGFR_{cys}$ ≈ $eGFR_{cr}$	Quartile 4 $eGFR_{cys}$ > $eGFR_{cr}$
N	158,601	39,651	39,650	39,650	39,650
Range, %	−83 to 133	−83 to −28	−27 to −10	−9 to 5	6 to 133
Age, y	62 ± 18	74 ± 15	65 ± 17	57 ± 18	53 ± 16
Female	48%	52%	48%	50%	42%
$eGFR_{cr}$, mL/min/1.73 m^2	80 ± 26	71 ± 25	78 ± 26	88 ± 25	81 ± 22
$eGFR_{cys}$, mL/min/1.73 m^2	73 ± 31	42 ± 17	64 ± 22	87 ± 25	97 ± 25
% $eGFR_{diff}$	−10 [−27 to 6]	−39 [−47 to −33]	−18 [−23 to −14]	−2 [−6 to 2]	17 [11 to 28]
KDIGO G groups by $eGFR_{cr}$					
eGFR 90+ mL/min/1.73 m^2	39%	26%	38%	55%	37%
eGFR 60-89 mL/min/1.73 m^2	38%	39%	36%	30%	48%
eGFR 45-59 mL/min/1.73 m^2	12%	18%	13%	7.9%	7.8%
eGFR 30-44 mL/min/1.73 m^2	7.1%	12%	8.3%	4.3%	3.4%
eGFR 15-29 mL/min/1.73 m^2	3.2%	5.0%	3.8%	2.0%	2.1%
eGFR <15 mL/min/1.73 m^2	0.70%	0.26%	0.51%	0.57%	1.5%
UACR, mg/g	12 [4-64]	28 [8-140]	14 [4-75]	8 [3-36]	6 [2-30]
Missing UACR	63%	62%	61%	63%	65%
Comorbidities					
Hypertension	59%	79%	67%	49%	39%
Diabetes mellitus	18%	27%	21%	15%	10%
Coronary heart disease	16%	27%	18%	11%	7.8%
Stroke	7.4%	14%	8.0%	4.4%	2.8%
Heart failure	11%	24%	10%	4.5%	3.0%
Peripheral arterial disease	2.9%	5.9%	3.0%	1.5%	1.1%
Atrial fibrillation	13%	24%	14%	7.9%	5.9%
Liver disease	3.1%	5.4%	3.1%	2.2%	1.6%
Recent cancer	16%	24%	18%	13%	9.6%
COPD	5.9%	12%	6.2%	3.5%	1.8%
Medications					
Hypertension meds	55%	75%	63%	46%	37%
RAS inhibitors	38%	48%	45%	33%	26%
Diuretics	28%	48%	32%	19%	14%
Statin	24%	29%	29%	22%	17%

Values for continuous variables given as mean ± SD or median [IQR]; for categorical variables as count (percentage). Abbreviations: COPD, chronic obstructive pulmonary disease; cr, creatinine; cys, cystatin C; eGFR, estimated glomerular filtration rate; RAS, renin angiotensin system; UACR, urinary albumin to creatinine ratio.

Table 2. Adjusted Hazard Ratios for Outcomes Associated With Quartiles of $eGFR_{diff}$

	Quartile 1 $eGFR_{cys} << eGFR_{cr}$	Quartile 2 $eGFR_{cys} < eGFR_{cr}$	Quartile 3 $eGFR_{cys} \approx eGFR_{cr}$	Quartile 4 $eGFR_{cys} > eGFR_{cr}$
Quartiles of Percent $eGFR_{diff}$				
$eGFR_{diff}$ range, %	−83 to −28	−27 to −10	−9 to 5	6 to 133
Hazard ratio (95% CI)				
KFRT	1.36 (1.17-1.58)	1.08 (0.94-1.25)	Ref	0.79 (0.69-0.92)
AKI	2.62 (2.42-2.85)	1.53 (1.40-1.67)	Ref	0.67 (0.59-0.75)
ASCVD	1.42 (1.33-1.51)	1.19 (1.11-1.27)	Ref	0.79 (0.73-0.86)
Heart failure	2.04 (1.92-2.17)	1.33 (1.25-1.41)	Ref	0.76 (0.70-0.83)
CVD death	2.48 (2.32-2.66)	1.40 (1.30-1.50)	Ref	0.85 (0.77-0.94)
All-cause death	2.62 (2.54-2.72)	1.46 (1.41-1.52)	Ref	0.80 (0.77-0.84)
Quartiles of Absolute $eGFR_{diff}$				
Absolute $eGFR_{diff}$ range, mL/min/1.73 m²	−118 to −19	−18 to −7	−6 to 4	5 to 87
Hazard ratio (95% CI)				
KFRT	2.46 (1.98-3.05)	1.20 (1.05-1.36)	Ref	0.57 (0.48-0.69)
AKI	3.10 (2.85-3.36)	1.60 (1.48-1.72)	Ref	0.64 (0.57-0.72)
ASCVD	1.46 (1.37-1.56)	1.19 (1.12-1.26)	Ref	0.78 (0.72-0.85)
Heart failure	2.20 (2.07-2.34)	1.41 (1.34-1.49)	Ref	0.73 (0.67-0.80)
CVD death	2.87 (2.69-3.06)	1.50 (1.41-1.58)	Ref	0.78 (0.70-0.86)
All-cause death	2.88 (2.79-2.98)	1.49 (1.45-1.54)	Ref	0.74 (0.70-0.77)

Quartiles 1 and 2 include participants in whom their $eGFR_{cys}$ was lower than $eGFR_{cr}$. Quartile 3 (reference) includes participants in whom $eGFR_{cys}$ and $eGFR_{cr}$ were similar. Quartile 4 depicts participants with $eGFR_{cys}$ higher than $eGFR_{cr}$. Adjusted for age, sex, hypertension, diabetes, history of CVD, $eGFR_{cr}$ (splines with knots at 60 and 90 mL/min/1.73 m^2), and UACR (logged). Abbreviations: AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; cr, creatinine; CVD death, cardiovascular-related death; cys, cystatin C; eGFR, estimated glomerular filtration rate; KFRT, kidney failure replacement therapy; MACE, major adverse cardiovascular events; Ref, reference value.

Pressure Intervention Trial (SPRINT)[28] (n = 9,092), the mean $eGFR_{diff}$ was −0.5 (± 15 SD) mL/min/1.73 m^2, and in the Cardiovascular Health Study (CHS)[11] (n = 4,635), −1.4 (± 14 SD) mL/min/1.73 m^2. The proportion of people with $eGFR_{diff}$ larger than 15 mL/min/1.73 m^2 in those studies ranged between 8% and 16%.[10,11,28] Because cystatin C testing is indicated in situations where creatinine is suspected to be inaccurate,[6] our study may inflate the range of $eGFR_{diff}$ observed in a nonselected general population. Our results underscore the common occurrence and extent of these situations in outpatient care, which may pose challenges in clinical decision making. We note that $eGFR_{diff}$ may be larger still in inpatient settings: in an evaluation of 841 patients from 3 trials of patients with acute decompensated heart failure, negative $eGFR_{diff}$ was progressively larger for each day longer of hospital stay.[29]

Our study suggests that the predictors of negative $eGFR_{diff}$ include older age and presence of comorbidities. One hypothesis is that these factors affect non-GFR determinants of serum concentrations of creatinine and cystatin C in different ways: older age and poor health status tend to result in lower creatinine for the same level of GFR, likely due to low muscle mass,[2-5] whereas cystatin C can be elevated for the same level of GFR in the setting of chronic inflammation. As shown in our study, $eGFR_{diff}$ were more negative at higher $eGFR_{cr}$ values, which may reflect the capture of frail individuals with inappropriately low serum creatinine. In addition, more negative $eGFR_{diff}$ was associated with the presence of albuminuria, similar to a CKD cohort, where discordances were related to UPCR. An alternative hypothesis by Grubb[13] is that selective reduction of $eGFR_{cys}$ depicted by an $eGFR_{cys}/eGFR_{cr} < 0.8$, equivalent to a negative $eGFR_{diff}$ equal or larger to 20%, reflects selective impairment of glomerular sieving of cystatin C and other middle molecular weight macromolecules (approximately 10,000-20,000 daltons) as an early manifestation of CKD, which is associated with adverse outcomes ("shrunken pore syndrome").[30]

We show that in situations of discordance a lower $eGFR_{cys}$ than $eGFR_{cr}$ identifies patients at higher risk of adverse outcomes. Our observational study cannot dissect whether risk associations are attributed to more accurate estimation of measured GFR by $eGFR_{cys}$, non-GFR determinants affecting $eGFR_{cr}$ and $eGFR_{cys}$, selective impairment of glomerular sieving of cystatin C, or a combination of these factors. Irrespective of the cause, it is likely that at least some of the risk associated with $eGFR_{diff}$ reflects health conditions that predict poor outcomes beyond GFR. Although theoretically accounting for non-GFR factors in estimating equations should abrogate any difference between $eGFR_{cr}$ and $eGFR_{cys}$, accurately measuring and quantifying all these factors is impractical and likely impossible in clinical practice. Thus, a non-zero $eGFR_{diff}$ indicates that one or both equations does not accurately account for these potential factors.

Our comprehensive outcome analysis largely agrees with studies in research cohorts and trials that have shown negative $eGFR_{diff}$ or $eGFR_{cys}/eGFR_{cr}$ ratios < 0.8[8-17] as being strongly associated with a range of outcomes,

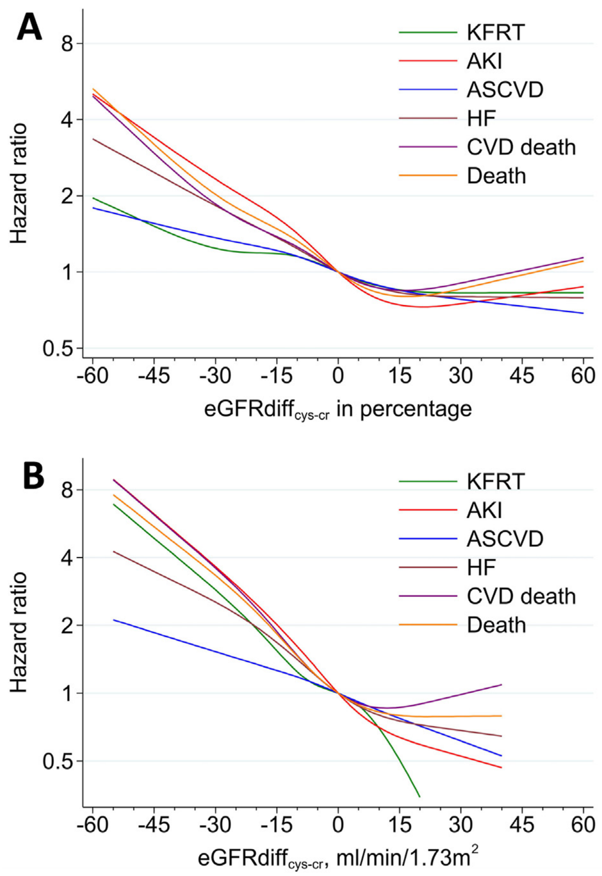

Figure 3. Lower $eGFR_{cys}$ compared with $eGFR_{cr}$ corresponds to higher risk across a range of outcomes. Adjusted hazard ratios for the association between percent and absolute difference $eGFR_{diff}$ with a range of clinical outcomes. The *x*-axis was truncated at 1% and 99% of $eGFR_{diff}$. For the outcome of KFRT, we further truncated at +20 mL/min/1.73 m^2 of absolute difference due to <10 events with an $eGFR_{diff}$ larger than this threshold. Abbreviations: AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; cr, creatinine; CVD death, cardiovascular-related death; cys, cystatin C; HF, heart failure; KFRT, kidney failure with replacement therapy.

although our larger sample size probably allowed for these associations to be more linear and of stronger magnitude. Given that large discrepancies were common and meaningful for prognosis, health systems may want to consider testing cystatin C more commonly in high-risk populations.

Key limitations of our study are the lack of information on reasons for obtaining tests of kidney function and on measured GFR, precluding an assessment of which eGFR is more accurate, and on potential confounders such as body mass index, muscle mass, or inflammation. Another limitation is the lack of information on race. Thus, our findings may be limited in terms of generalizability to other world regions with larger ethnic variation.

To conclude, cystatin C testing in routine Swedish care demonstrated that many patients have discordant $eGFR_{cys}$ and $eGFR_{cr}$, and that lower $eGFR_{cys}$ than $eGFR_{cr}$ is associated with worse clinical outcomes. As for clinical implications, these findings offer support to the use of cystatin C testing in health care,[1] highlighting the prognostic relevance of assessing both $eGFR_{cys}$ and $eGFR_{cr}$ rather than relying only on $eGFR_{cr}$. Because higher risks were consistently observed for $eGFR_{diff}$ throughout all stages of $eGFR_{cr}$, evaluating $eGFR_{diff}$ can be useful for risk stratification, monitoring health status, and prompting clinical actions.

Supplementary Material

Supplementary File (PDF)

Figure S1: Flow chart of patient inclusion into the study.

Figure S2: Univariate correlation between percent and absolute $eGFR_{diff}$ and 4×4 contingency table across quartiles of absolute and percent $eGFR_{diff}$.

Table S1: Definition of study covariates and outcomes.

Table S2: Baseline characteristics by quartiles of absolute $eGFR_{diff}$.

Table S3: Logistic regression model with robust estimators of conditions associated with quartiles of percent $eGFR_{diff}$.

Table S4: Logistic regression model with robust estimators of conditions associated with quartiles of absolute $eGFR_{diff}$.

Table S5: Subgroup analyses for the association between $eGFR_{diff}$ and AKI.

Table S6: Subgroup analyses for the association between $eGFR_{diff}$ and KFRT.

Table S7: Subgroup analyses for the association between $eGFR_{diff}$ and ASCVD.

Table S8: Subgroup analyses for the association between $eGFR_{diff}$ and heart failure.

Table S9: Subgroup analyses for the association between $eGFR_{diff}$ and CVD death.

Table S10: Subgroup analyses for the association between $eGFR_{diff}$ and all-cause death.

Table S11: *P* values for interaction across subgroups for the association between $eGFR_{diff}$ and outcomes.

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