Discordance in creatinine based eGFR and cystatin C based eGFR and clinical outcomes

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Word count: Abstract 321 Main text 3123

Abstract:

Importance: Estimated glomerular filtration rates (eGFRs) can differ according to whether creatinine or cystatin C is used for the eGFR calculation, but frequency and importance of such differences remain poorly understood.

Objectives: To evaluate the prevalence of a discordance between cystatin C (eGFRcys) and creatinine-based eGFR (eGFRcr), identify characteristics associated with greater likelihood of discordance, and evaluate associations of discordance with adverse outcomes.

Design, setting, and participants: Individual-level data meta-analysis of participants in the CKD Prognosis Consortium who had concurrent cystatin C and creatinine measurements.

Main outcomes: The primary outcome was a large negative eGFR difference (eGFRdiff), defined as an eGFRcys that was at least 30% lower than eGFRcr. Secondary outcomes included all-cause and cardiovascular mortality, atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and kidney failure requiring replacement therapy (KFRT).

Results: 821,327 individuals were included from 23 ambulatory cohorts (mean age 59 [SD 12] years, 48% female, 13.5% diabetes, 40% hypertension), and 36,639 individuals were included from two inpatient cohorts (mean age 67 [SD 16] years, 31% female, 30% diabetes, 72% hypertension). Among ambulatory participants, 11% had a large negative eGFRdiff (range across cohorts: 3%-50%). Among inpatients, 35% had a large negative eGFRdiff. With a mean follow-up of 11 years (SD 4), a large negative eGFRdiff was associated with higher rates of all-cause mortality (HR=1.69; 95%CI: 1.57-1.82, 28.5 vs. 16.9 per 1000 person-years), cardiovascular mortality (HR=1.61; 95%CI: 1.48-1.76, 6.1 vs. 3.8 per 1000 person-years), ASCVD (HR=1.35; 95%CI: 1.27-1.44, 13.3 vs. 9.8 per 1000 person-years), HF (HR=1.54; 95%CI: 1.40-1.68, 13.2 vs. 8.6 per 1000 person-years) and KFRT (HR=1.29; 95%CI: 1.13-1.47, 2.7 vs. 2.1 per 1000 person-years).

Conclusions and relevance: In the CKD Prognosis Consortium, 11% of ambulatory participants and 35% of hospitalized patients had an eGFRcys that was at least 30% lower than eGFRcr. In the ambulatory setting, presence of eGFRcys at least 30% lower than eGFRcr was associated with significantly higher rates of all-cause mortality, cardiovascular events, and kidney failure.

KEYPOINTS

Question: Do people whose eGFR calculated using cystatin C is at least 30% lower than their eGFR calculated using creatinine have higher rates of adverse outcomes, compared to people whose eGFR calculated using cystatin C is similar to their eGFR using creatinine?

Findings: In this individual participant-level meta-analysis that included 821,327 participants from 23 ambulatory cohorts and 36,639 participants from 2 inpatient cohorts, eGFRcys was at least 30% lower than eGFRcr in 11% of ambulatory and 35% of hospitalized participants. Among ambulatory participants, those with an eGFRcys at least 30% lower than eGFRcr compared to participants without an eGFRcys vs. eGFRcr difference had significantly higher mortality (28.5 vs. 16.9 per 1000 person-years), atherosclerotic cardiovascular events (13.3 vs. 9.8 per 1000 person-years), and kidney failure requiring therapy (2.7 vs. 2.1 per 1000 person-years) at 11 years of follow-up.

Meaning: In the ambulatory and inpatient settings, an eGFRcys value that is at least 30% lower than eGFRcr was common, and in the ambulatory setting, was associated with higher rates of adverse outcomes.

INTRODUCTION

Chronic kidney disease (CKD) diagnosis, staging and treatment partially rely on estimated glomerular filtrate rate (eGFR).[1] eGFR calculations are most often based on blood creatinine (Cr) as the filtration marker. However, Cr levels are affected by factors that alter muscle metabolism, such as diet and physical activity,[2] and medications that impair tubular creatinine secretion. Cystatin C (CysC) is a different filtration marker that is not affected by muscle or secreted by the tubules, but its levels may be affected by characteristics such as smoking, obesity and inflammation.[2] Multiple studies have demonstrated that eGFR based on both Cr and CysC better reflects kidney function.[1] However, non-kidney influences may also contribute to substantial differences between eGFR based on Cr (eGFRcr) versus CysC (eGFRcys), which in turn may have prognostic implications.[3-7] These analyses sought to: 1) characterize the prevalence of large eGFRcys and eGFRcr differences in cohorts within the CKD Prognosis Consortium (CKD-PC) overall and across eGFRcr levels in both the ambulatory and inpatient settings; 2) identify factors associated with having discordant eGFRcys and eGFRcr; and 3) evaluate whether large eGFRcys and eGFRcr differences are prognostic of adverse cardiovascular and kidney outcomes in the ambulatory setting.

METHODS

Participating Cohorts and Study Design

The CKD-PC includes clinical, research, and trial cohorts which ascertained kidney measures and longitudinal outcomes.[8] For this study, cohorts were invited if their participants had Cr and CysC measurements on the same day (**Appendix 1**); 23 cohorts met inclusion criteria and agreed to participate (**Appendix 2**). Analyses were limited to participants aged ≥18 years, with non-missing age, sex, and same-day Cr and CysC. The Institutional Review Board at New York University Grossman School of Medicine waived the need for informed consent and approved this study.

Analyses were performed among participating ambulatory cohorts (a mix of clinical, research and trial cohorts) and inpatient cohorts (clinical cohorts only), separately. The frequency of CysC measures in these different settings are reported in **Appendix 1**. Only ambulatory cohorts were included in the evaluation of the association of eGFRcys and eGFRcr differences at baseline with longitudinal outcomes; the first visit for each

person with available concurrent Cr and CysC was considered the baseline in each cohort.

Kidney Measures and Calculation of eGFR Differences

Appendix 1 describes methods for Cr and CysC measurements. Cohorts measured Cr using methods traceable to IDMS-standard, and most measured CysC calibrated or standardized to International Federation for Clinical Chemists (IFCC) standards.[9,10] eGFRcr and eGFRcr-cys were estimated using the 2021 race-free CKD-EPI equations[11] and eGFRcys using the 2012 CKD-EPI equation.[12]

Primary analyses focused on large negative eGFR differences (eGFRdiff), defined as an eGFRcys at least 30% lower than eGFRcr (*i.e.* ([eGFRcys – eGFRcr]/eGFRcr) < -30%). Thirty-percent was chosen as the threshold because it is the established cutoff for determining the accuracy of eGFR equations.[11] As secondary analysis, large negative eGFRdiff was defined as an eGFRcr-cys at least 15% lower than eGFRcr. Since clinical actions often rely on the KDIGO GFR ("G") staging for CKD,[1] reclassification to a worse eGFR category using eGFRcys versus eGFRcr was also examined. Additional analyses included evaluating a large positive eGFRdiff, defined as an eGFRcys or eGFRcr-cys 30% or 15% higher than eGFRcr, respectively.

Covariate Definitions

Factors with known associations with eGFRdiff or hypothesized to influence Cr or CysC concentrations independent of GFR were evaluated as covariates,[13-15] including: 1) sociodemographic and lifestyle variables (age, sex, and smoking status); 2) comorbidities (history of coronary heart disease, stroke, heart failure [HF], atrial fibrillation, peripheral artery disease [PAD], cancer, chronic obstructive pulmonary disease [COPD], and liver disease); and 3) clinical measures (body mass index [BMI] and albumin-to-creatinine ratio [ACR]). Obesity was defined as a BMI ≥30 kg/m^2. ACR was natural log-transformed, and missing ACR was analyzed as a separate binary category among clinical cohorts.

To harmonize data elements across cohorts, the CKD-PC Data Coordinating Center (DCC) provided definitions to participating cohorts in the data request. **Appendix 1** details the ascertainment and missingness of each variable. In clinical datasets, comorbidity was defined by the presence of two ICD-9 or ICD-10 diagnosis codes in the ambulatory setting within 730 days or of one inpatient/problem list diagnosis code prior to the kidney measures. Cohorts were asked to specify if they utilized alternative variable definitions.

Longitudinal Outcomes

All-cause mortality, cardiovascular mortality, atherosclerotic cardiovascular disease (ASCVD) events, incident heart failure (HF), and kidney failure with replacement therapy (KFRT) were obtained from ambulatory cohorts. **Appendix 1** details cohort-specific outcome definitions. U.S.-based cohorts ascertained KFRT via linkage to the U.S. Renal Data System[16] unless otherwise noted. For the remaining outcomes, some cohorts identified outcomes based on diagnosis codes while others employed additional clinical adjudication for specific outcomes.

Statistical Analyses

Descriptive statistics and kernel-density plots were performed for the overall distributions of eGFRcr, eGFRcys, eGFRcr-cys and eGFRdiff and of participant characteristics within cohorts. The proportion of participants with a large negative eGFRdiff, by eGFRcr category, was summarized as the median (25^{th} and 75^{th} percentile) across ambulatory cohorts and as the range between the two inpatient cohorts.

A logistic regression model was constructed to estimate the odds ratio (OR) and 95% confidence interval (95% CI) of having a large negative eGFRdiff compared to an eGFRdiff of -30% to 30%. Within each cohort, if a variable was unavailable or missing in more than 50% of the participants, the variable was not included in the model; otherwise, missing values were imputed with the mean. A similar analysis was performed for the odds ratios associated with reclassification to a worse eGFR category. The adjusted odds of a large negative eGFRdiff was estimated in each in-house cohort using the meta-analyzed odds ratios and summarized as median (25^{th} and 75^{th} percentile) across ambulatory cohorts and as the range between the two inpatient cohorts.

Within each ambulatory cohort, Cox proportional hazards models were used to evaluate the association of eGFRdiff with long-term risks of adverse outcomes; random-effects models were employed to meta-analyze hazard ratios (HR). eGFRdiff was modeled both as a continuous (linear splines with knots at -30%, -15%, 0%, and 30%) and categorical variable (*e.g.* large negative eGFRdiff, small eGFRdiff [reference], or positive eGFRdiff). Models adjusted for age; female sex; smoking status; history of hypertension, diabetes, coronary heart disease, stroke, HF, atrial fibrillation, PAD, cancer, COPD, or liver disease; BMI (spline knot at 30 kg/m^2),

eGFRcr category; and log-ACR (a missing indicator was also included in clinical studies) (**Appendix 1**). Sensitivity analyses stratified by cohort types to examine variability across general population, clinical and CKD cohorts in forest plots as well as analyses excluding the bank were conducted. To demonstrate adjusted incidence rates of adverse outcomes in the presence or absence of a large eGFRdiff, the ARIC cohort was used to estimate rates for a baseline scenario at the mean of the overall population.

Analyses were conducted using Stata/MP version 18.

RESULTS

Study Population

The 23 ambulatory cohorts comprised 821,327 individuals while the two inpatient-based cohorts included 39,639 individuals.

Among ambulatory participants at baseline, the mean (standard deviation [SD]) age was 59 (12) years; 48% were female; 13.5% had diabetes; and 40% had hypertension (**Table 1**). The proportion of participants with CysC measurements within the total population with Cr measurements in each cohort ranged from 1.9% to 100% in the ambulatory cohorts (**Appendix 1**). The overall mean eGFRcr and eGFRcys among ambulatory participants were 87 (22), and 81 (25) ml/min/1.73 m^2, respectively (**Table 2**), with an overall median eGFRdiff of -5.4% (Interquartile interval [IQI]: -15.3%, 2.9%). Approximately 11.2% had a large negative eGFRdiff; only 3.8% had a large positive eGFRdiff. The eGFRdiff distribution varied across ambulatory cohorts (**Figure 1**), with the proportion of participants having a large negative and positive eGFRdiff ranging from 2.8% to 49.8% and 0% to 27.9%, respectively. The overall mean eGFRcr-cys was 86 (23), and the median eGFRdiff between eGFRcr-cys and eGFRcr was 0.5% (IQI: -5.8%, 5.6%) among ambulatory participants (**Supplemental Table 1** and **Supplemental Figure 1**).

Table 1 summarizes the baseline characteristics among inpatients. Their mean age was 67 (16) years; 31% were female; 30% had diabetes; and 72% had hypertension. In the two inpatient cohorts, the proportion of hospitalizations with Cr values and concurrent CysC measurements was 0.7% and 6.6% (**Appendix 1**). The overall mean eGFRcr, eGFRcys were 69 (32) and 57 (33) ml/min/1.73 m^2, respectively (**Table 2**) among inpatients, with a median eGFRdiff of -15.4% and -29.1% in the two cohorts. Approximately 35% of inpatients had a large negative eGFRdiff, and 14.5% had a large positive eGFRdiff. The mean eGFRcr-cys was 63 (33),

and median eGFRdiff when comparing eGFRcr-cys with eGFRcr values were -6.5% and -16.1% in the two cohorts, respectively (**Supplemental Table 1**).

Percentage of Participants with a Large Negative eGFRdiff by eGFRcr Categories

Table 3 shows the percentage of individuals who have a large negative eGFRdiff within each eGFRcr category, summarized across cohorts. Among ambulatory studies, the median percentage was generally greater at lower eGFRcr values. For example, within the eGFRcr of 90+ and 60-89 ml/min/1.73 m^2 categories, the median percentages were both 7.8%, while they were 12.3%, 17.6% and 14.8% within the 45-59, and 30-44 and <30 ml/min/1.73 m^2 categories, respectively. Compared with the ambulatory setting, percentages of individuals with a large negative eGFRdiff were higher within inpatient cohorts (**Table 3**), ranging from 22.5% to 57.2%, 41.1% to 57.0%, and 23.8% to 24.4% among those with an eGFRcr of 90+, 45-59, and <30 ml/min/1.73 m^2, respectively.

The percentage reclassified to a lower eGFR category was notably higher in the inpatient than in the ambulatory setting (**Table 3**). For instance, among those with an eGFRcr of 45-59 ml/min/1.73 m^2, the median percentage reclassified was 34.0% in the ambulatory setting whereas it ranged from 63.9% to 76% in the inpatient setting. Percentages evaluating eGFRcr-cys relative to eGFRcr followed a similar pattern (**Supplemental Table 2**).

Characteristics Associated with eGFRdiff

In the ambulatory setting, the estimated prevalence of a large negative eGFRdiff for a 70-year-old male with hypertension, diabetes, no smoking or other comorbidities, eGFRcr of 45-59 ml/min/1.73 m^2, ACR of 30 mg/g, and BMI of 30 kg/m^2 was 8.8% (IQI: 6.7%, 20.7%). Characteristics most strongly associated with a large negative eGFRdiff included current smoking (OR=2.09 [1.59, 2.74], 16.7% vs. 8.8%), HF (OR=1.81 [1.53, 2.14], 14.8 vs. 8.8%), and liver disease (OR=1.79 [1.12, 2.88], 14.7% vs. 8.8%). Older age (OR=1.68 per 10 years older [1.55, 1.81], 13.9% vs. 8.8%), COPD (OR=1.61 [1.38, 1.89], 13.4% vs. 8.8%), PAD (OR=1.60 [1.48, 1.74], 13.4% vs. 8.8%), and BMI (OR=1.53 per 5 kg/m^2 higher [1.37, 1.69], 12.8% vs. 8.8%) had more modest associations (**Table 4**). Relative to an eGFRcr of 45-59 ml/min/1.73 m^2, higher eGFRcr categories were associated with greater likelihood, while lower eGFRcr categories were associated with lower likelihood of a large negative eGFRdiff. For example, an eGFRcr ≥90 ml/min/1.73 m^2 was associated with a 1.56- fold

(1.14, 2.14) higher odds (13.0% vs. 8.8%) while an eGFRcr <30 ml/min/1.73 m^2 was associated with 0.56-fold (0.46, 0.69) lower odds (5.1% vs. 8.8%) of a large negative eGFRdiff. Similar associations were observed when eGFRdiff was based on eGFRcr-cys relative to eGFRcr and when odds of downward eGFR-staging was the outcome (**Supplemental Table 3**).

In the inpatient setting, the estimated prevalence for the same above scenario was 38.1% and 43.8% in the two cohorts. Characteristics associated with higher likelihood of a large negative eGFRdiff in the inpatient setting were largely like those in the ambulatory setting. For example, HF (OR=1.63 [1.21, 2.19], 53% vs. 41%) and liver disease (OR=1.74 [1.25, 2.41], 55% vs. 41%) remained strongly associated with a large negative eGFRdiff **(Table 4)**; older age, diabetes, PAD, and COPD were also associated, with ORs of 1.18 to 1.38. eGFR categories <45 ml/min/1.73 m^2 were associated with incrementally lower odds of a large negative eGFRdiff versus an eGFR of 45-59 ml/min/1.73 m^2 (eGFR 30-44: OR=0.79 [0.64, 0.98], 36% vs. 41% and eGFR <30: OR=0.33 [0.17, 0.64], 19% vs. 41%). Associations were qualitatively similar when eGFRdiff was based on eGFRcr-cys relative to eGFRcr and when odds of downward shift to a lower eGFR category was the outcome (**Supplemental Table 3**).

eGFRdiff and mortality in the ambulatory cohorts

During a mean follow-up of 11 (4) years, 107,584 and 25,465 all-cause and cardiovascular deaths occurred, respectively; 35,133; 34,017; and 10,060 ASCVD, HF and KFRT events occurred, respectively (**Supplemental Table 4**). **Figure 2** shows the HR for each outcome across the range of eGFRdiff; progressively larger negative eGFRdiff was associated with increasingly greater risk for every adverse outcome.

Compared to an eGFRdiff of -30 to 30%, a large negative eGFRdiff was associated with higher risks for all-cause mortality (HR=1.69 [1.57, 1.82] , 28.5 vs. 16.9 per 1000 person-years), cardiovascular mortality (HR=1.61 [1.48, 1.76] , 6.1 vs. 3.8 per 1000 person-years), ASCVD (HR=1.35 [1.27, 1.44] , 13.3 vs. 9.8 per 1000 person-years), HF (HR=1.54 [1.40, 1.68] , 13.2 vs. 8.6 per 1000 person-years), and KFRT (HR=1.29 [1.13, 1.47] , 2.7 vs. 2.1 per 1000 person-years) (**Supplemental Table 5**). Participants with a large positive eGFRdiff had lower risks for all-cause mortality (HR=0.76 [0.73, 0.80]. 12.9 vs. 16.9 per 1000 person-years), cardiovascular mortality (HR=0.79 [0.67, 0.91], 3.0 vs. 3.8 per 1000 person-years), ASCVD (HR=0.81 [0.74,

0.89], 8.0 vs. 9.8 per 1000 person years), HF (HR=0.76 [0.69, 0.84], 6.5 vs. 8.6 per 1000 person years), and KFRT (HR=1.04 [0.84, 1.29, 2.1 vs. 2.1 per 1000 person-years]). Risk estimates were similar when UK Biobank data were excluded **(Supplemental Table 5**). Each association also remained robust within cohort types (**Supplemental Figure 2)**.

Secondary analyses using eGFRcr-cys rather than eGFRcys in calculating eGFRdiff yielded similar results (**Supplemental Figure 3** and **Supplemental Table 6**)**.**

DISCUSSION

A large proportion of the >800,000 participants had an eGFRcys substantially lower than eGFRcr. The magnitude of the eGFRdiff and percentage of individuals with a large negative eGFRdiff were notably greater in the inpatient cohorts compared with the ambulatory cohorts. Relative to eGFRcr, use of eGFRcys reclassified large proportions of individuals to a worse GFR stage. Factors associated with a large negative eGFRdiff included age, smoking and several comorbidities and were similar between the ambulatory and inpatient settings. In addition, a large negative eGFRdiff portended higher risks for all-cause and cardiovascular mortality, ASCVD, HF and KFRT. These findings highlight how frequently large discordances occur between GFR estimates based on Cr alone and those that incorporate CysC; they provide convincing evidence that a large negative eGFRdiff identifies individuals who carry significantly elevated risks for cardiovascular and kidney outcomes.

Nearly all prior studies of eGFRdiff examined only ambulatory populations and relied on single cohorts.[3-6,17] They consistently found a ~30% prevalence of discordant eGFRcr and eGFRcys, with the proportion having a large negative eGFRdiff varying from as low as 8% in a CKD cohort[3] to 16% in an elder population.[17] To our knowledge, only one prior study included hospitalized patients.[18] Among the 684 hospitalized patients examined previously, the median eGFRdiff was -18 versus 4 mL/min/1.73 m^2 in 1,367 ambulatory individuals. The present analysis builds upon these prior findings through comprehensive analysis of participant-level data from 23 ambulatory cohorts and evaluation of two large inpatient cohorts. Consistent with prior literature, the proportion of individuals with a large negative eGFRdiff varied widely across the CKD-PC cohorts, ranging from 3% to 50%, and were much higher in the inpatient versus ambulatory settings. Inter-cohort differences in the

proportion of participants with clinical characteristics associated with eGFRdiff may explain the varied prevalence of a large negative eGFRdiff across studies and between inpatient and ambulatory settings.

Prior studies have also shown that persons with a large negative eGFRdiff are at higher risk of all-cause mortality,[3,6] ASCVD,[6,19] incident HF[4,6], and KFRT.[6] Findings from the present study align with these previous observations and substantiate that eGFRdiff offers prognostic information beyond eGFRcr. This added prognostic information likely captures risk associated with “true GFR” and factors associated with worse outcomes which either lower Cr, such as frailty, or increase CysC, such as inflammation.

This study has several clinical implications. First, results from this study imply that CysC testing identifies a large number of individuals who may have worse kidney function than would be implied by eGFRcr alone and who would require a better estimate of kidney function for clinical decision-making. In the ambulatory setting, this would be most accurately estimated using eGFRcr-cys;[11] however, robust evidence on which eGFR estimating equation is most accurate in the inpatient setting remains lacking. The large percentage of hospitalized patients with a large negative of eGFRdiff underscores the need for additional studies with directly measured GFR in the inpatient setting to address this knowledge gap. Second, the findings suggest that CysC testing among older individuals, those with key comorbid conditions, or hospitalized patients would offer the highest yield of identifying a large negative eGFRdiff and individuals who may be re-staged to a lower eGFR category. Identifying large differences between eGFRcys and eGFRcr is especially critical in patients with moderate to advanced CKD and among hospitalized patients since they are often prescribed medications that require dose adjustments. Third, the eGFRdiff provides inherent prognostic information on important clinical outcomes and supports laboratory reporting of eGFRcys and eGFRcr-cys alongside eGFRcr as large differences may identify patients at higher risk of adverse long-term outcomes.

Limitations

This study has several limitations. First, other GFR-estimating equations were not evaluated; however, eGFRdiff arises primarily from factors that affect Cr or CysC beyond adjustment variables used in the equations. Although the prevalence of eGFRdiff may differ based on the equations used; the patterns of eGFRdiff predictors will likely be robust. Second, residual calibration differences for Cr or CysC could explain some variation among studies. Third, study designs and outcome ascertainment protocols differed across cohorts, and outcomes were largely based on diagnosis codes. Fourth, as inpatient cohorts were clinical,

potential selection bias as to who underwent CysC testing may exist. Fifth, data were lacking on additional non-GFR factors like muscle mass or thyroid disorders or factors unique to the inpatient setting that may affect Cr or CysC levels. Sixth, the UK Biobank comprised approximately half of the ambulatory study population and was predominantly White race (>90%); however, sensitivity analyses that excluded data from UK Biobank yielded associations of large eGFRdiff with outcomes similar to the main analyses. Last, participants with CysC measurements available and included in the study represented a minority of otherwise eligible patients who had Cr measurements in clinical cohorts and are likely not representative of these cohorts' overall study populations. However, analyses stratified by cohort type showed robust associations across cohort types.

Conclusion

In the CKD Prognosis Consortium, 11% of ambulatory participants and 35% of hospitalized patients had an eGFRcys that was at least 30% lower than eGFRcr. In the ambulatory setting, presence of eGFRcys at least 30% lower than eGFRcr was associated with significantly higher rates of all-cause mortality, cardiovascular events, and kidney failure.

ACKNOWLEDGMENTS

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Data Sharing Statement: Under agreement with the participating cohorts, CKD-PC cannot share individual data with third parties. Inquiries regarding specific analyses should be made to ckdpc@nyulangone.org. Investigators may approach the original cohorts regarding their own policies for data sharing (e.g., https://aric.cscc.unc.edu/aric9/researchers/Obtain_Submit_Data for the Atherosclerosis Risk in Communities Study).

Disclosures: MME has served on advisory boards for AstraZeneca and Boehringer Ingelheim and has a collaborative research agreement with Bayer; all are unrelated to the present work. JA has received lecturing fees from AstraZeneca and Boehringer Ingelheim and served on advisory boards for AstraZeneca, Boehringer Ingelheim and Astella, all unrelated to the present project. JJC reports grants paid to Karolinska Institutet from AstraZeneca, Boehringer Ingelheim, CSL Vifor, MSD, Astellas, NovoNordisk, all outside the submitted work; personal fees for lectures or advisory board meetings from Fresenius Kabi, and Laboratorios Columbia, all outside the submitted work. J.S.L. has received personal lectureship honoraria from AstraZeneca and consultancy fees from Boehringer Ingelheim outside the submitted work.

Some of the data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

Funding: The CKD Prognosis Consortium (CKD-PC) Data Coordinating Center is funded in part by a program grant from the US National Kidney Foundation and the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK100446). A variety of sources have supported enrollment and data collection including laboratory measurements, and follow-up in the collaborating cohorts of the CKD-PC. These funding sources include government agencies such as national institutes of health and medical research councils as well as foundations and industry sponsors listed in Supplemental Appendix 3. DLC receives funding from the NIDDK (5U01DK060984-25). JSL received funding from Wellcome Trust Early Career Award (301005/Z/23/Z). The funding sources did not have a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Table 1: Sociodemographic and clinical characteristics of participants overall and within each cohort for ambulatory and inpatient settings

Cohort	N	Converted ACR	Age	Female	DM	HTN	BMI	Former smoker	Current smoker	CHD	Stroke	HF	Afib	PAD	Cancer	COPD	Liver Disease
Overall Ambulatory	**821,327**	**9 (6-18)**	**59 (12)**	**48%**	**13.5%**	**40%**	**28 (5)**	**36%**	**12%**	**8.8%**	**3.7%**	**4.4%**	**5.7%**	**1.2%**	**12%**	**4.3%**	**3.2%**
ICKD	930	160 (40-628)	49 (12)	33%	36%	95%	25 (5)	13%	15%	4.3%				0.54%	0.11%		0.11%
CKD Rein	3,031	112 (22-516)	67 (13)	35%	43%	95%	29 (6)	47%	12%	25%	7.4%	11%	11%	16.9%	21%	10%	1.8%
ULSAM	1,103	8 (5-17)	71 (1)	0%	13%	77%	26 (3)		21%	8.2%	3.0%	1.6%	4.7%	0.54%	6.6%		1.3%
VA	90,526	21 (7-99)	65 (14)	10%	48%	78%	32 (7)	42%	13%	30%	5.7%	15%	14%	3.7%	19%	18%	13%
SCREAM	151,502	12 (7-29)	62 (18)	48%	18%	59%				16%	7.4%	11%	13%	2.9%	16%	5.9%	3.1%
Takahata	1,339	9 (6-17)	64 (10)	56%	8.5%	57%	23 (3)	10%	15%	3.4%	1.1%						
CRIB	362	429 (89-1202)	61 (14)	35%	18%	94%	27 (5)	50%	13%	19%	7.5%						
MDRD	1,044	114 (10-769)	52 (13)	39%	9.6%	74%	27 (4)		10%	9.8%	2.2%			3.8%			
ESTHER	9,759	Dipstick	62 (7)	55%	19%	60%	28 (5)	33%	16%	9.1%	3.4%	10%	0.73%	1.6%	7.8%	1.0%	
REGARDS	28,035	7 (5-16)	66 (9)	55%	21%	59%	29 (10)	40%	14%		6.2%						
GCKD	5,175	51 (10-392)	61 (12)	40%	36%	96%	30 (6)	73%	26%	20%	8.3%	19%	21%	7.5%	12%	6.9%	4.5%
FRAMINGHAM	2,596	6 (3-15)	59 (10)	54%	8.8%	39%	28 (5)		15%	3.6%	0.19%	0.81%					
CRIC	5,485	46 (8-368)	60 (11)	44%	51%	87%	32 (8)	42%	13%		10%	9.7%			8.4%	5.5%	
NHANES	4,960	8 (5-18)	56 (21)	50%	17%	53%	28 (6)	43%	12%	10%	5.2%	4.8%					
ARIC	11,303	4 (2-8)	63 (6)	56%	17%	48%	29 (6)	44%	15%	8.6%	2.3%	5.7%	1.9%	3.5%			
CHS	3,377	10 (5-23)	78 (5)	60%	17%	50%	27 (5)	44%	7%	24%	6.2%	9.3%		3.2%			
MASTERPLAN	477	120 (28-482)	60 (13)	31%	23%		27 (4)		17%	20%	7.3%						
PREVEND	7,940	7 (5-13)	50 (13)	50%	3.9%	34%	26 (4)	37%	34%	4.4%	0.92%	0.29%					
UK BioBank	467,963	9 (6-18)	57 (8)	54%	4.7%	27%	27 (5)	35%	10%	3.9%	1.6%	0.062%	1.5%	0.26%	8.7%	1.0%	
AASK	949	12 (5-130)	55 (11)	39%	0%	100%	31 (7)	29%	29%	44%	10%	2.6%		3.4%			
MESA	6,770	5 (3-11)	62 (10)	53%	13%	45%	28 (5)	37%	13%	0%	0%	0%	0%	0.059%	8.6%		6.5%
AUSDIAB	10,558	5 (4-9)	52 (14)	55%	6.4%	32%	27 (5)	29%	16%	6.6%	2.5%						
Uonuma	6,143	11 (6-25)	68 (10)	51%	9.7%	51%	23 (3)	31%	14%		0.42%		1.9%		9.4%	0%	
Overall Inpatient	**39,639**	**18 to 56**	**67 (16)**	**31%**	**30%**	**72%**	**27 (7)**	**49%**	**20%**	**42%**	**12%**	**27%**	**24%**	**7.8%**	**28%**	**17%**	**11%**
VA IP	9,372	56 (12-321)	72 (12)	5.7%	51%	86%	27 (7)	49%	20%	53%	14%	38%	30%	13%	37%	37%	27%
SCREAM IP	30,267	18 (12-90)	65 (17)	39%	24%	68%				38%	12%	23%	22%	6.2%	25%	11%	6.2%

Results presented as mean (standard deviation), percentages, or median (interquartile range).
Abbreviations: ACR, albumin-to-creatinine ratio; DM, diabetes mellitus; HTN, hypertension; BMI, body mass index; CHD, coronary heart disease; HF, heart failure; Afib, atrial fibrillation; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease. Blank boxes indicate where data were not available. Any cells with <11 participants do not include data linked to USRDS.

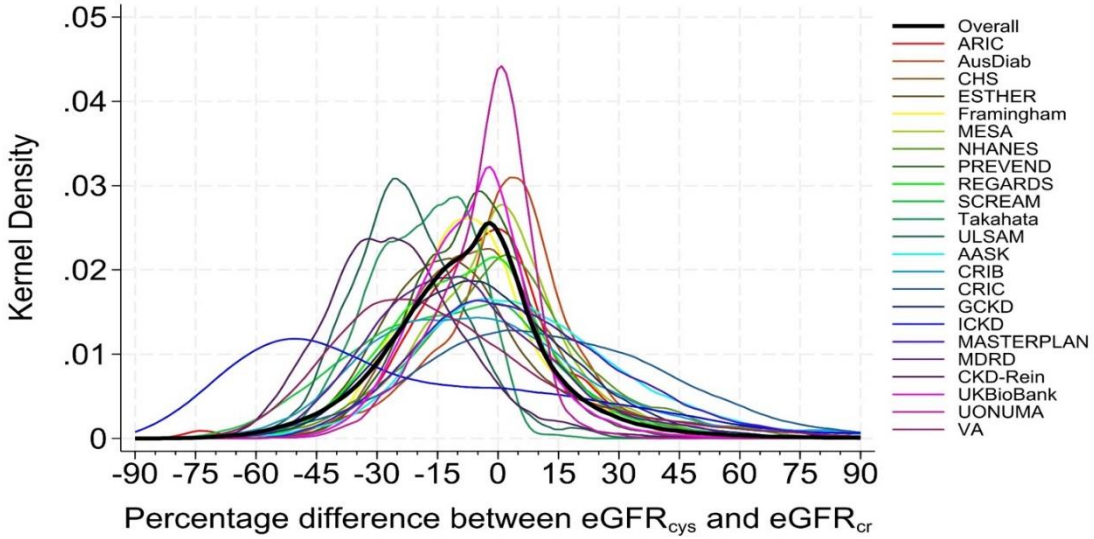
Table 2. Distribution of eGFR and eGFRdiff in the outpatient and inpatient settings, overall and by cohort

Cohort	No. of participants included	eGFRcr	eGFRcys	(eGFRcys-eGFRcr)/eGFRcr,%	(eGFRcys-eGFRcr)/eGFRcr <-30%	(eGFRcys-eGFRcr)/eGFRcr >30%
Overall Ambulatory	**821,327**	**87 (22)**	**81 (25)**	**-5.4 (-15.3 to 2.9) ***	**92,154 (11.2%)**	**31,024 (3.8%)**
ICKD	930	47 (17)	40 (31)	-29.7 (-52.2 to 10.2)	463 (49.8%)	151 (16.2%)
CKD Rein	3,031	36 (14)	27 (11)	-26.3 (-36.7 to -15.2)	997 (41.4%)	17 (0.7%)
ULSAM	1,103	81 (11)	62 (13)	-23.5 (-31.4 to -13.9)	328 (29.7%)	3 (0.3%)
VA	90,526	67 (25)	58 (27)	-16.9 (-32.1 to 2.4)	25,641 (28.4%)	7,781 (8.6%)
SCREAM	151,502	80 (26)	73 (31)	-9.8 (-27.5 to 6.0)	35,102 (21.9%)	7,857 (5.2%)
Takahata	1,339	101 (11)	82 (18)	-17.6 (-28.1 to -8.6)	279 (20.8%)	0%
CRIB	362	23 (12)	21 (12)	-6.6 (-23.7 to 12.0)	57 (15.7%)	42 (11.6%)
MDRD	1,044	36 (16)	32 (14)	-10.7 (-23.6 to 4.1)	158 (15.1%)	56 (5.4%)
ESTHER	9,759	87 (20)	80 (16)	-9.9 (-21.9 to 4.8)	1,175 (12.0%)	1,026 (10.5%)
REGARDS	28,035	84 (19)	78 (23)	-6.7 (-20.3 to 5.4)	3,178 (11.5%)	1,104 (3.9%)
GCKD	5,175	52 (19)	50 (20)	-5.1 (-19.0 to 9.8)	544 (10.6%)	3,76 (7.3%)
FRAMINGHAM	2,596	92 (17)	85 (18)	-7.7 (-18.1 to 2.4)	217 (8.4%)	81 (3.1%)
CRIC	5,485	48 (16)	54 (23)	10.5 (-9.3 to 32.9)	427 (7.8%)	1,528 (27.9%)
NHANES	4,960	87 (25)	88 (30)	1.2 (-12.4 to 14.0)	365 (7.4%)	533 (10.7%)
ARIC	11,303	88 (16)	84 (19)	-3.3 (-15.0 to 7.0)	732 (6.5%)	565 (5.0%)
CHS	3,377	69 (16)	66 (18)	-5.0 (-16.6 to 7.1)	207 (6.1%)	174 (5.2%)
MASTERPLAN	477	38 (16)	40 (19)	3.2 (-11.9 to 21.0)	27 (5.7%)	87 (18.2%)
PREVEND	7,940	100 (15)	93 (19)	-6.2 (-16.7 to 2.7)	441 (5.6%)	103 (1.3%)
UK BioBank	467,963	95 (13)	89 (16)	-5.4 (-15.3 to 2.9)	20,845 (4.5%)	8,652 (1.8%)
AASK	949	42 (13)	45 (18)	4.8 (-10.9 to 22.8)	43 (4.5%)	167 (17.6%)
MESA	6,770	90 (16)	89 (20)	-0.2 (-11.7 to 9.6)	298 (4.4%)	364 (5.4%)
AUSDIAB	10,558	99 (17)	100 (23)	2.6 (-7.3 to 11.0)	460 (4.4%)	343 (3.2%)
Uonuma	6,143	95 (12)	92 (18)	-1.6 (-10.2 to 4.2)	170 (2.8%)	14 (0.2%)
Overall Inpatient	**39,639**	**69 (32)**	**57 (33)**	**-29.1 to -15.4***	**13,866 (35%)**	**5,747 (14.5%)**
VA IP	9,372	58 (32)	41 (26)	-29.1 (-46.0 to -8.3)	4901 (52.6%)	708 (7.6%)
SCREAM IP	30,267	73 (32)	62 (34)	-15.4 (-33.7 to 2.8)	8,965 (29.6%)	5,039 (16.6%)

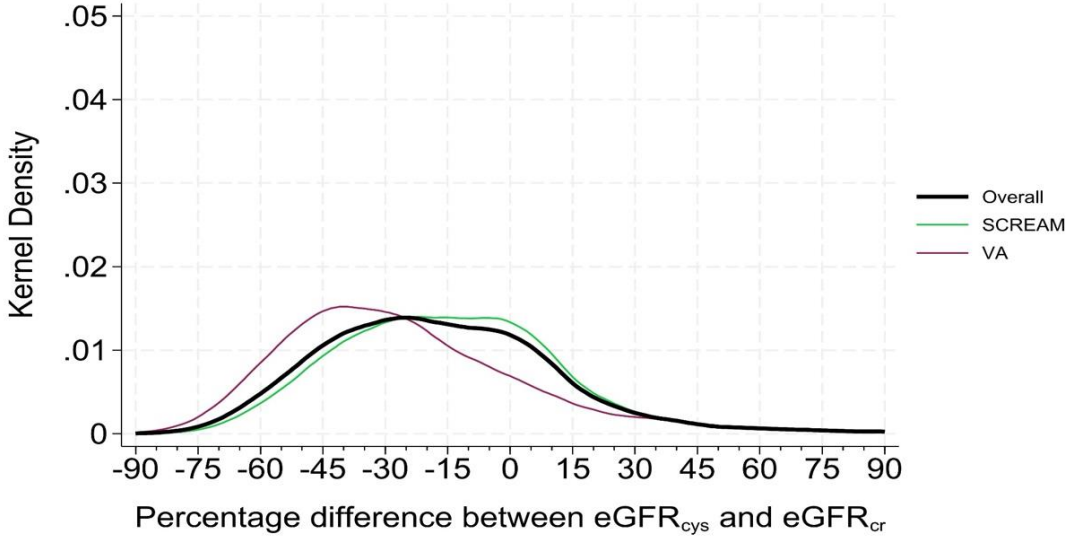
Note: Table presents data only from participants included in the analyses. Results presented as mean (standard deviation) or percentages. eGFR difference percentage reflects the median cohort and 25th and 75th percentile cohort for outpatient, and the range of the two cohorts for inpatient. Any cells with <11 participants do not include data linked to USRDS.

Figure 1. Distribution of the percentage difference between eGFRcys and eGFRcr, across each cohort

A. Ambulatory Cohorts



B. Inpatient Cohorts



Note: eGFRdiff calculated as (eGFRcys – eGFRcr)/eGFRcr

Table 3. Observed percentage of individuals who have a large negative eGFR difference or are reclassified to a worse eGFR category with eGFRcys relative to eGFRcr, by eGFRcr category

	eGFRcr 90+	eGFRcr 60-89	eGFRcr 45-59	eGFRcr 30-44	eGFR <30
	AMBULATORY Median percentage across cohorts (25th to 75th percentile) *				
N	455,258	260,629	52,426	33,209	16,556
(eGFRcys – eGFRcr)/eGFRcr < -30%	7.8 (4.0 to 17.9)	7.8 (5.8 to 23.3)	12.3 (7.1 to 27.0)	17.6 (6.2 to 29.4)	14.8 (9.2 to 31.9)
Reclassified to a worse eGFR category with eGFRcys relative to eGFRcr	45.2 (29.0 to 63.3)	16.1 (12.7 to 36.2)	34.0 (22.4 to 58.5)	28.3 (18.8 to 41.7)	NA
	INPATIENT Percentage range of two cohorts				
N	13,055	10,972	4,840	4,652	6,120
(eGFRcys – eGFRcr)/eGFRcr < -30%	22.5 to 57.2	32.1 to 63.0	41.1 to 57.0	41.1 to 49.5	23.8 to 24.4
Reclassified to a worse eGFR category with eGFRcys relative to eGFRcr	45.3 to 79.0	46.2 to 75.9	63.9 to 75.9	56.5 to 65.2	NA

Notes: *The median (25th to 75th percentile) was the raw percentage summarized across cohorts (CKD cohorts were excluded from eGFRcr 90+ and 60-89 due to small sample size)

Abbreviations: eGFRcys, cystatin C-based estimated glomerular filtration rate; eGFRcr, creatinine-based estimated glomerular filtration rate. Both in ml/min/1.73 m^2

Table 4. Associations of participant characteristics with a large negative eGFR difference between eGFRcys and eGFRcr

	AMBULATORY	INPATIENT
	OR (95% CI)	OR (95% CI)
Age, per 10y older	1.68 (1.55, 1.81)	1.27 (1.21, 1.33)
Female	1.17 (1.10, 1.24)	1.07 (0.80, 1.43)
Hypertension	1.12 (1.02, 1.22)	1.04 (0.97, 1.11)
Diabetes mellitus	1.15 (1.08, 1.23)	1.18 (1.12, 1.25)
Non-smoker	Reference	Reference
Former smoker	1.03 (0.95, 1.11)	1.21 (1.09, 1.34)
Current smoker	2.09 (1.59, 2.74)	1.04 (0.91, 1.19)
Coronary heart disease	1.20 (1.11, 1.30)	0.78 (0.60, 0.99)
Stroke	1.23 (1.07, 1.42)	1.13 (0.88, 1.46)
Heart failure	1.81 (1.53, 2.14)	1.63 (1.21, 2.19)
Atrial fibrillation	1.20 (1.09, 1.33)	1.09 (0.95, 1.26)
Peripheral arterial disease	1.60 (1.48, 1.74)	1.38 (1.12, 1.69)
Cancer	1.14 (1.01, 1.29)	1.25 (1.03, 1.51)
Chronic obstructive pulmonary disease	1.60 (1.48, 1.74)	1.36 (1.24, 1.50)
Liver disease	1.79 (1.12, 2.88)	1.74 (1.25, 2.41)
BMI <30, per 5 kg/m^2 higher	1.06 (0.89, 1.27)	0.98 (0.92, 1.04)
BMI ≥30, per 5 kg/m^2 higher	1.53 (1.37, 1.69)	1.20 (1.12, 1.28)
eGFRcr 90+	1.56 (1.15, 2.10)	0.92 (0.55, 1.52)

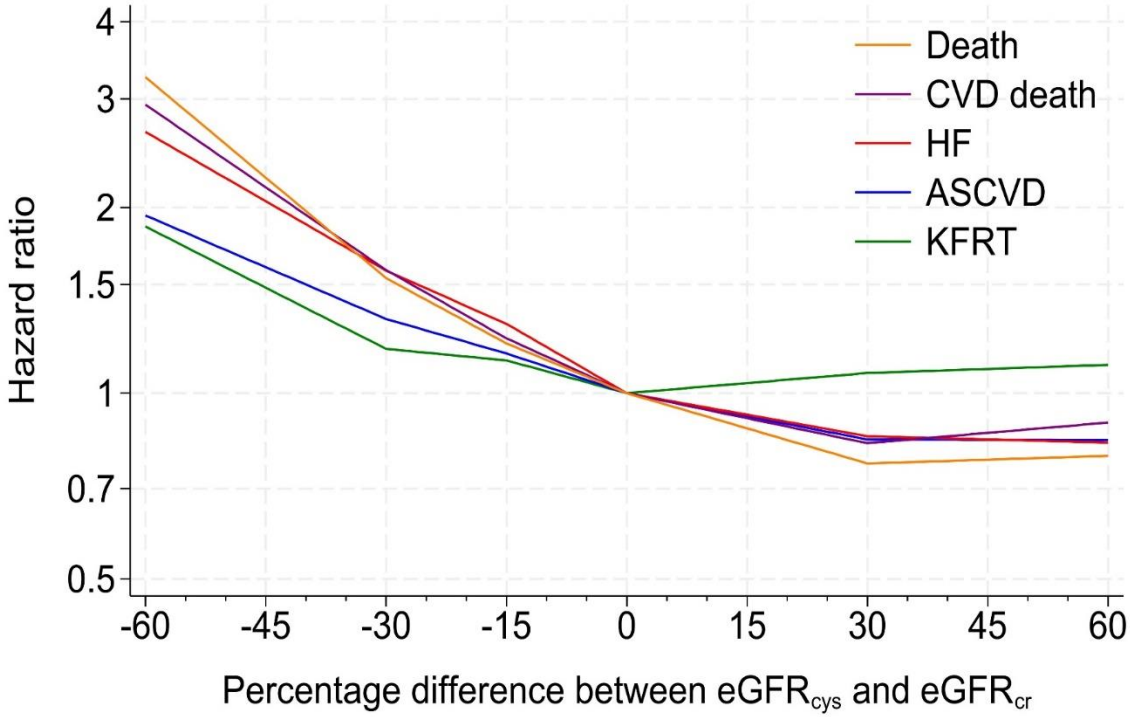
eGFRcr 60-89	1.23 (1.06, 1.44)	1.08 (0.67, 1.74)
eGFRcr 45-59	Reference	Reference
eGFR 30-44	0.89 (0.78, 1.01)	0.79 (0.64, 0.98)
eGFR <30	0.56 (0.46, 0.69)	0.33 (0.17, 0.64)
lnACR, per e-fold higher	1.17 (1.14, 1.20)	1.06 (0.99, 1.13)

Notes: Large negative eGFRdiff defined as ([eGFRcys – eGFRcr]/eGFRcr) < -30%. Models adjusted for all variables listed.

Abbreviations: OR, odds ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate in ml/min/1.73 m^2; ACR, urine albumin-to-creatinine ratio

The prevalence of a large eGFRdiff for a 70-year-old man with hypertension, diabetes, no smoking or other comorbidities, eGFR 45-59 ml/min/1.73 m^2, ACR 30 mg/g, BMI 30 kg/m^2 was 8.8% (6.7%, 20.7%) in the outpatient and 38.1% - 43.8% in the inpatient cohorts. We used the median (25^{th} – 75^{th}) adjusted prevalence for outpatient and range for inpatient across cohorts combined with the meta-analyzed odds ratios.

Figure 2. Association of the percentage difference between eGFRcys and eGFRcr and risks of long-term adverse outcomes in the ambulatory setting



Note: eGFRdiff calculated as (eGFRcys – eGFRcr)/eGFRcr and modeled as a linear spline with knots at -30%, -15%, 0%, and 30%.

Models adjusted for age, sex, hypertension, diabetes, former and current smoking, history of coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, cancer, liver disease, chronic obstructive pulmonary disease, body mass index (linear splines with knot at 30), eGFRcr categories (G1, G2, G3a, G3b, G4&5), ACR missing indicator (only for clinical cohort), log-UACR. Linear splines were also used for eGFRdiff

Abbreviations: eGFRcys, cystatin C-based estimated glomerular filtration rate; eGFRcr, creatinine-based estimated glomerular filtration rate; CVD, cardiovascular disease; HF, heart failure; ASCVD, atherosclerotic cardiovascular disease; KFRT, kidney failure requiring therapy