Estimating GFR Among Participants in the Chronic Renal Insufficiency Cohort (CRIC) Study

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Abstract

Background—Glomerular filtration rate (GFR) is considered the best measure of kidney function, but repeated assessment is not feasible in most research studies.

Study Design—Cross-sectional study of 1,433 participants from the Chronic Renal Insufficiency Cohort (CRIC) Study (i.e., the GFR subcohort) to derive an internal GFR estimating equation using a split sample approach.

Setting & Participants—Adults from 7 US metropolitan areas with mild to moderate chronic kidney disease; 48% had diabetes and 37% were black.

Index Test—CRIC GFR estimating equation

Reference Test or Outcome—Urinary ^{125}I-iothalamate clearance testing (measured GFR)

Other Measurements—Laboratory measures including serum creatinine and cystatin C, and anthropometrics

Results—In the validation dataset, the model that included serum creatinine, serum cystatin C, age, gender, and race was the most parsimonious and similarly predictive of mGFR compared to a

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model additionally including bioelectrical impedance analysis phase angle, CRIC clinical center, and 24-hour urinary creatinine excretion. Specifically, the root mean square errors for the separate model were 0.207 vs. 0.202, respectively. The performance of the CRIC GFR estimating equation was most accurate among the subgroups of younger participants, men, non-blacks, non-Hispanics, those without diabetes, those with body mass index <30 kg/m^2, those with higher 24-hour urine creatinine excretion, those with lower levels of high-sensitivity C-reactive protein, and those with higher mGFR.

Limitations—Urinary clearance of ^{125}I-iothalamate is an imperfect measure of true GFR; cystatin C is not standardized to certified reference material; lack of external validation; small sample sizes limit analyses of subgroup-specific predictors.

Conclusions—The CRIC GFR estimating equation predicts measured GFR accurately in the CRIC cohort using serum creatinine and cystatin C, age, gender, and race. Its performance was best among younger and healthier participants.

Index words

glomerular filtration rate (GFR); kidney function; GFR estimation

An extensive body of information suggests that glomerular filtration rate (GFR) is the best overall index of kidney function.[1-3] GFR is operationally measured as the clearance rate of a filtration marker from the plasma by the kidneys, but clearance tests are cumbersome and costly. In clinical practice and large-scale research projects, more convenient methods, such as determinations of serum creatinine and timed urinary creatinine clearance, have been used for diagnosis of reduced kidney function and for monitoring disease progression.[4-10] However, factors other than GFR, including the production, tubular secretion, and extrarenal elimination of creatinine influence the serum concentration of this compound. Therefore, use of serum creatinine or creatinine clearance determinations alone may not always accurately estimate kidney function.[1-3;7;8;10]

GFR estimating equations that include demographic parameters and serum creatinine are available online, and are used extensively clinically and in research studies.[6;11-13] Incorporation of measures of body size, creatinine generation, inflammation, and/or cystatin C into these estimating equations may address some of the limitations of serum creatinine-based equations. Improvements in GFR estimation were reported in several populations using equations that incorporate both serum creatinine and cystatin C.[14-16]

One of the main objectives of the ongoing National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored Chronic Renal Insufficiency Cohort (CRIC) Study is to improve the accuracy of assessing the level of kidney function and monitoring chronic kidney disease (CKD) progression within the cohort. As annual measurement of GFR was infeasible, this goal will be accomplished through GFR estimation. While existing GFR estimating expressions such as the Modification of Diet in Renal Disease (MDRD) Study equation and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are used widely in clinical and research settings,[11;13;16] their performance in the CRIC Study population may be limited due to differences in entry criteria between participants in CRIC and other studies, use of non-uniform GFR measurements, and limited sets of predictors. The objective of the current analysis was to utilize an extensive set of standardized data to derive an internal GFR estimating equation with optimal performance characteristics for future use in CRIC, describing the patterns of decline in kidney function in the entire cohort. Additionally, we compared the performance of the CRIC GFR estimating equation across study participant subgroups.

Methods

Participants

Study Population—The CRIC Study is a multi-center prospective cohort study of 3,939 racially and ethnically diverse adults aged 21 to 74 years old at baseline with mild to moderate CKD; 45% were female, 48% had diabetes, 42% were black, and 13% were Hispanic. Participants were recruited from clinical centers in Philadelphia, PA, Baltimore, MD, Cleveland, OH, Detroit, MI, Chicago, IL, New Orleans, LA, and Oakland, CA from June 2003 through September 2008. Inclusion was based on age-specific estimated GFR (eGFR) cutpoints calculated using the four-variable MDRD Study equation.[11] The study design, methods, and baseline characteristics of the cohort have been described in detail elsewhere.[17-19] Approximately one-third of the CRIC cohort (i.e., the GFR subcohort; N=1433) was selected, using stratified sampling by age, gender, race, diabetes status, MDRD Study equation eGFR, and CRIC clinical center, to have GFR measured at baseline, Year 2, and Year 4 study visits; data from these participants at baseline are used in the current analysis.

Data Collection—Numerous serum and urine measures are relevant to the current analysis beyond serum creatinine and serum cystatin C including: serum albumin (dye-binding assay), serum urea nitrogen, and plasma glucose (Hitachi Vitros 950 AT, www.roche.com); total plasma homocysteine (Abbott AxSYM, www.abbott.com); high-sensitivity C-reactive protein (hsCRP; Siemens BN™ II System, www.medical.siemens.com); plasma brain natriuretic protein (BNP), plasma fibrinogen, and urine neutrophil gelatinase-associated lipocalin (NGAL; Abbott Architect ci8200, www.abbott.com); insulin (Perkin-Elmer Gamma Counter, www.perkinelmer.com); interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and interleukin 1 receptor-antagonist (IL-1ra) (Beckman Coulter FXp/Paradigm plate reader, www.beckmancoulter.com); 24-hour urine creatinine (Bio-Tek Plate Reader ELX 808, www.biotek.com); 24-hour urine total protein (Roche/Hitachi Modular P Chemistry Analyzer, www.roche.com); urine protein-creatinine ratio; 24-hour urine albumin (Siemens Immulite, www.medical.siemens.com); 24-hour urine urea nitrogen (Catachem, Inc. endpoint spectrophotometric assay, www.catacheminc.com); and creatinine clearance calculated using the Cockcroft-Gault formula.[20] Most of these assays were batched and run after all baseline visits were completed. Insulin resistance and insulin sensitivity were estimated using homeostasis model assessment (HOMA) equations (HOMA-IR and SI-HOMA, respectively).[21]

Race and ethnicity were self-reported; diabetes mellitus was defined as a fasting plasma glucose 126 mg/dL or a non-fasting plasma glucose 200 mg/dL, or self-report of anti-diabetes medication use. Height was measured using a wall-mounted stadiometer, weight was measured using either balanced beam scale or regularly-calibrated electronic digital scale, and waist circumference was measured using a Gulick II or Gulick II Plus anthropometric tape measure just above the uppermost lateral border of the ilium.[22] Body mass index (BMI) was calculated as weight in kg/square of height in meters. Bioelectrical impedance analysis (BIA) measures including resistance and reactance were taken using the Quantum II analyzer. BIA phase angle and impedance were calculated from resistance and reactance using standard equations.[23] Fat-free mass was computed from gender-specific equations using weight, height, and resistance.[24]

Test Methods

Reference Standard—GFR was measured using a standardized protocol for urinary ^{125}I-iothalamate clearance testing after a low-protein (<10 g) meal.[25-27] The test was chosen due to its comparability to inulin clearance testing, and prior use in other NIDDK-sponsored

major research studies.[25;26] Exclusions for the ^{125}I-iothalamate test were known iodine allergy, impaired urinary voiding, current breastfeeding or pregnancy, thallium stress test in the past 30 days, self-catheterization, renal replacement therapy, inadequate venous access, and radiation exposure to γ-emitting isotope other than technetium. Plasma and urine radioactive counts were analyzed at the Central GFR Laboratory for the CRIC Study (Cleveland Clinic Foundation, Cleveland, OH). Measured GFR (mGFR) was calculated with and without exclusion of the first clearance period due to concerns regarding systematic elevations during this period, and adjusted to 1.73 m^2 of body surface area (BSA).[26] Mean mGFR was 1.0 mL/min/1.73m^2 lower overall with, compared to without, exclusion of the first clearance period. Due to increased precision of mGFR values with exclusion of the first clearance period, this measure was used as the reference standard in the analysis.

Index Tests—Serum creatinine assays were enzyme-based for all baseline visits and performed on the Hitachi Vitros 950 AT (www.roche.com; CV of 1.1%). Serum creatinine values were calibrated to standardized values at the Cleveland Clinic Research Laboratory (Cleveland, OH).[28] Serum cystatin C was measured in stored baseline specimens using a particle-enhanced immunonephelometric assay on the Siemens BN™ II System (www.siemens.com) with a CV of 4.9%. An internal CRIC cystatin C standardization was implemented to correct for drift over time when using different calibrator lots and reagent lots.[29]

Statistical Methods

Descriptive Statistics—Baseline characteristics of the overall CRIC cohort, the GFR subcohort, and cohort members not included in the subcohort are described using means +/- standard deviations (SD) or medians (25th-75th percentiles) for continuous variables, and counts and percentages for categorical variables. Differences between the GFR subcohort and remaining participants were compared using the chi-square test for categorical variables and t-test for continuous variables. Median mGFR intra-test coefficients of variation (CV) were computed overall, and by CRIC clinical center and level of GFR. All factors with skewed distributions were log-transformed, including serum creatinine and cystatin C. Bivariate associations of characteristics with mGFR, before and after adjustment for age, gender, and race, were examined using linear regression models.

Model Development—CRIC GFR subcohort members at baseline were randomly divided into two groups; two-thirds (n=949) were used to derive a GFR estimating equation (development dataset), which was subsequently validated among the remaining one-third (n=484; validation dataset). Using the development dataset, an extensive set of candidate variables were explored as predictors of mGFR. These included fixed variables (gender, race, Hispanic ethnicity, and diabetes at study entry), variables available at all visits (set A: serum creatinine, serum cystatin C, serum albumin, serum urea nitrogen, age, height, weight, BMI, waist circumference, urine creatinine concentration, BIA resistance and reactance, fat-free mass, impedance, and BIA phase angle), and variables not available at all visits (set B: 24-hour urine protein, 24-h urine creatinine, 24-hour urine protein-creatinine ratio, 24-hour urine albumin, 24-hour urine urea nitrogen, plasma glucose, total plasma homocysteine, hsCRP, BNP, fibrinogen, insulin, creatinine clearance, HOMA-IR, SI-HOMA, IL-6, TNF-α, IL-1ra, and urine NGAL). Given the primary purpose of the equation is for CRIC internal use, CRIC clinical center was also considered as a predictor. Model selection was performed using linear regression models of natural log-transformed mGFR to satisfy the stable variance assumption of the model, and a forward selection strategy. Serum creatinine (log-transformed), age, gender and race were forced into the model. We first restricted the model building using set A predictors only. At each step, a single factor was added into the model that most improved the model fit measured by R^2. Model-building stopped when no further

variables had p-values < 0.01. Next, we explored set B factors as additional predictors using the same stepwise approach.

Once model-building was completed, the regression coefficients, root mean square error (RMSE) and R^2 for each stepwise model were compared. Nonlinear relationships of the two key predictors of serum creatinine and cystatin C with mGFR were explored graphically and by adding higher-order terms into the models. Spline terms were explored, when appropriate. Knots for serum creatinine values at 0.7 and 0.9 mg/dL for women and men, respectively, from the CKD-EPI serum creatinine equation were not assessed given the lack of values below that range in the current population.[13] Separate models in diabetic and non-diabetic groups were also fit and the coefficients for serum creatinine and cystatin C were compared. Formal tests of interaction between diabetes and both serum creatinine and cystatin C were implemented using cross-product terms.

Model Evaluation—All candidate models generated from the development were compared for performance in the validation dataset overall and within subgroups defined by age, gender, race, ethnicity, diabetes, BMI, 24-hour urine creatinine excretion, hsCRP and mGFR level. Measures of performance included the median difference (the difference between measured and estimated GFR) and percent median difference (median difference divided by measured GFR); the inter-quartile ranges for the median difference and percent median difference; P_{30} (percent of estimated GFR within 30% of measured GFR); and root mean square error (RMSE). Bootstrap re-sampling with 1000 repeated samples was employed to calculate 95% confidence intervals. Because CRIC participants were not randomly selected into the GFR subcohort, participants were re-weighted with the inverse of the sampling probability of being selected into the subcohort for the final model (not shown).

Informed Consent and Regulatory Approval

All aspects of the current study were approved by the Institutional Review Boards for each CRIC participating site and the Scientific and Data Coordinating Center. Informed consent was obtained from all participants prior to the baseline study visit. This study also conformed to the Health Insurance Portability and Accountability Act guidelines.

Results

Baseline characteristics for the entire CRIC cohort, the GFR subcohort, and those not in the subcohort are presented in Table 1. The mean mGFR levels with and without exclusion of the first clearance period were 48.0 ±19.9 (SD) and 49.0 ±21.0 mL/min/1.73m², respectively. The median intra-test CV was 9.7% with exclusion of the first clearance period and 12.0% otherwise, and this measure varied by CRIC clinical center and level of kidney function. Among subcohort members, the mean age was 56.0 ±12.3 years; 43.8% were female and 48.1% had diabetes mellitus. Fifteen percent were Hispanic, and 37.3% reported black race. Median 24-hour urine protein excretion was 210.8 (25th-75th percentile, 76.5-1073.1) mg/d. The mean serum concentration of creatinine was 1.70 ±0.57 mg/dL and of cystatin C was 1.46 ±0.52 mg/L. Mean BMI was 31.3 ±6.9 kg/m² and BSA was 2.04 ± 0.27 m². Compared to the remainder of the CRIC Study cohort, subcohort members were younger, less likely to report black race, more likely to be Hispanic, and had lower levels of serum creatinine, cystatin C, plasma glucose, 24-hour urine albumin excretion, and urine NGAL. With the exception of weight, fat-free mass, and plasma glucose, all candidate predictors had a statistically significant relationship with mGFR after adjustment for age, gender, and race (Table 2).

Model Development

The regression coefficients and model fit of five equations derived in the development dataset are provided in Table 3. The addition of cystatin C into the model decreased the magnitude of all other coefficients by one-half compared to the model with serum creatinine alone. Subsequent additions of BIA phase angle, CRIC clinical center, and 24-hour urine creatinine excretion had little impact on the coefficients of the first five variables (i.e., serum creatinine, cystatin C, age, gender, and race).

The relationships of log(serum creatinine) and log(cystatin C) with ln(mGFR) were explored graphically and both appeared linear (Figure 1). Quadratic terms for serum creatinine and cystatin C, when added to the models, were not statistically significant. Given the strongly linear relationship and lack of significant quadratic terms for these predictors, no further exploration of non-linear relationships using spline terms was performed. The interaction terms between diabetes and both serum creatinine and cystatin C were not statistically significant.

Model Evaluation

In the validation dataset, the model incorporating both serum creatinine and cystatin C with age, gender, and race was unbiased, accurate, and had substantially better overall performance compared to the model with serum creatinine alone (Table 4). Performance of models was essentially unchanged after the addition of BIA phase angle, CRIC clinical center, and 24-hour urine creatinine excretion.

Due to the similarity in the performance of Models 2 through 5 in the validation dataset, the most parsimonious model including serum creatinine, cystatin C, age, gender, and race was chosen as the final model. Table 5 displays its performance in the validation dataset by subgroup. The CRIC GFR estimating equation was most accurate among younger participants, men, non-blacks, and non-Hispanics. In addition, equation accuracy declined among those with diabetes, obese participants, those with the least 24-hour urine creatinine excretion, those with high hsCRP, and participants with eGFR levels below 45 mL/min/1.73m^2.

Performance of the final CRIC GFR estimating equation by level of estimated GFR in the validation dataset is shown in Figure 2. The CRIC GFR estimating equation was unbiased across the range of estimated GFR.

Discussion

The CRIC Study is the largest prospective cohort study of CKD with detailed phenotypic assessment and measures of kidney function and cardiovascular disease. To achieve the aim of estimating GFR and tracking progression of CKD, a new CRIC GFR estimating equation was developed. After considering a broad set of candidate predictors including demographic and anthropometric measures, various biomarkers, and clinical characteristics, the final CRIC GFR estimating equation includes five variables; serum creatinine and cystatin C, and age, gender, and race. In the validation dataset, this equation demonstrated accuracy and precision similar to more complicated equations including BIA phase angle, CRIC clinical center, and 24-hour urine creatinine excretion, overall and within subgroups. Eighty-nine percent of estimated values were within 30% of measured GFR using the new equation. Compared across subgroups, the CRIC GFR estimating equation was most accurate among younger participants, men, non-blacks, non-Hispanics, those without diabetes, those with BMI < 30 kg/m^2, and those with the highest 24-hour urine creatinine excretion levels and lowest hsCRP levels. Finally, GFR was most accurately predicted among participants with eGFR 45 mL/min/1.73m^2.

Although GFR measurement using urinary ^{125}I-iothalamate clearance tests correlates well with clearance of the gold standard, inulin,[25;30-32] these tests have known substantial variability across clearance periods as evidenced by median CVs of 9.4% and 11.7% in the MDRD Study and the Diabetes Control and Complications Trial.[26] Additionally, levels of mGFR tend to decline across clearance periods, especially at higher levels of GFR, further increasing the variability of the measure.[26;33] In the CRIC Study, the goal to best characterize level of kidney function by both measured and estimated GFR motivated the exclusion of the first period of all clearance tests performed. Evidence of the success of this strategy was demonstrated by the increased precision of mGFR levels overall and a 1 mL/min/1.73m^2 correction of bias. However, even with these improvements, performance of the CRIC GFR estimating equation was very similar with and without the exclusion of the first clearance period (data not shown).

The motivation to develop a GFR estimating equation specific to the CRIC Study came, in part, from our effort to identify novel factors which may significantly improve GFR estimation. However, among over 20 novel factors considered, including measures of body composition, and inflammation, none substantively improved GFR estimation once factors included in the CKD-EPI joint serum creatinine-cystatin C estimating equation (i.e., serum creatinine, cystatin C, age, gender, and race) were included.[16] This was also true across all subgroups of interest included in our analyses, although small sample sizes in the validation dataset among subgroups limits our ability to compare equations (data not shown). The lack of additional informative predictors, along with the reduction in the coefficients for age, gender, and race once cystatin C was added to the model, supports recent findings that non-renal elimination of cystatin C may be minimal and that cystatin C levels may not be influenced by factors considered in the current analysis including level of inflammation.[34-36] However, elucidation of non-GFR determinants of cystatin C levels awaits further study. Our findings provide reassurance that the performance of the most commonly used GFR estimating equations is not limited by the set of predictors available in typical research and clinical settings.

Variability in CRIC GFR estimating equation performance was observed across all subgroups examined, but none of these differences reached a level of statistical significance. Despite this, notable improvements to GFR prediction were present among demographic subgroups including participants <45 years of age, men, non-blacks, and non-Hispanics. Additionally, GFR was least accurately predicted among the least healthy including those with diabetes, obese individuals, those with low 24-hour urine creatinine excretion, those with high levels of inflammation, and among participants with more advanced CKD. Much of this variability in equation performance by age, gender, race, diabetes status, and BMI may largely be explained by known differences in these populations with non-renal elimination and generation of serum creatinine. The relatively small number of participants in any given subgroup precluded further exploration of factors that may influence GFR prediction in these subpopulations.

The current study has several strengths including the size of the subcohort that underwent urinary ^{125}I-iothalamate clearance testing, allowing for large development and validation datasets. The goal of developing an internal equation allowed for the exploration of a varied set of candidate GFR predictors including body composition measures, and novel factors such as urine NGAL and insulin resistance. Another strength is the oversampling of non-Hispanic black/African-Americans and those with diabetes, and the inclusion of 215 Hispanics to generate a GFR estimating equation potentially more applicable in these subpopulations.

Our study had limitations as well. First, the CRIC Study equation was not developed to replace other published equations such as the CKD-EPI equation in the clinical setting.[11;13;16] The CRIC Study enrolled selected individuals with mild to advanced CKD, and findings may not be applicable to certain types of kidney disease that did not occur frequently in the cohort, such as polycystic kidney disease and glomerulonephritis. Additionally, the CRIC GFR estimating equation has not been externally validated. Second, although main effect and interaction terms were explored for certain subpopulations such as those with diabetes, small effects cannot be ruled out due to the numbers of participants in these subgroups. Third, although exclusion of the first mGFR clearance period increased precision and corrected bias, estimates arising from the CRIC GFR estimating equation versus existing equations generated using unaltered urinary ^{125}I-iothalamate clearance test data may not be entirely comparable. The impact of this is unlikely to be consequential owing to the principal goal of optimizing GFR estimation for use within the CRIC Study. Despite exclusion of the first clearance period, the precision of mGFR remained limited, potentially lowering accuracy of eGFR. Indeed, limitations to the precision of mGFR remain one of the largest barriers to improving GFR estimation.[37] Fourth, the GFR subcohort was comprised of a slightly different population compared to the full CRIC cohort. To address this concern, coefficients in the final CRIC GFR estimating equation used internally were weighted back to the characteristics of the full cohort using several demographic and clinical characteristics. Finally, an initial 19% drift in cystatin C values among healthy population control samples was observed,[29] necessitating that all cystatin C values be internally standardized to a specific calibrator and reagent lot. This limits the direct comparison of our data to other studies incorporating cystatin C data until CRIC's and other studies' values are standardized to certified reference material (ERM-DA471/IFCC).[38;39]

The CRIC GFR estimating equation provides accurate and unbiased GFR prediction within the CRIC study population, and will be used for estimating level of kidney function as well as trajectories of decline. While the CRIC estimating equation performs very well overall, accuracy declines among certain subgroups including older participants, women, blacks, those with diabetes, obese participants, those with higher levels of inflammation, and those with lower levels of kidney function.

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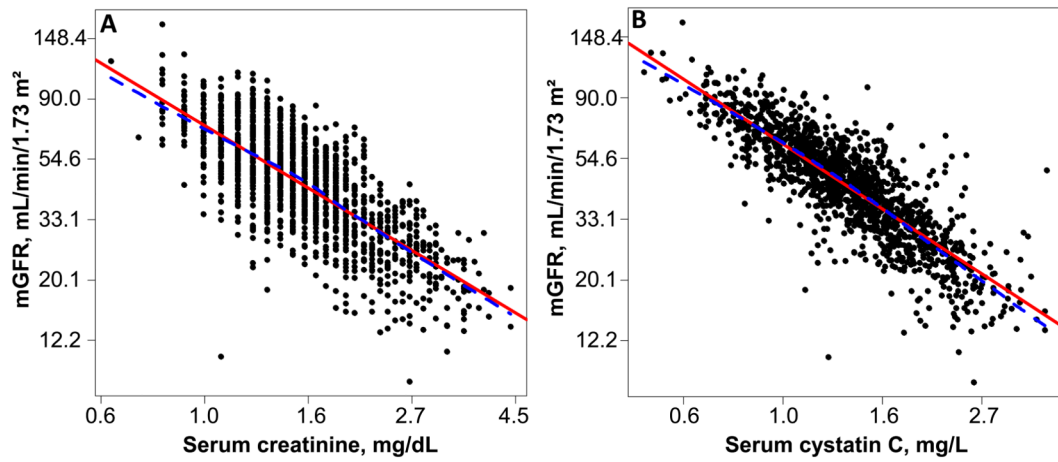
Figure 1.
Scat terplots of (A) mGFR with serum creatinine, and (B) mGFR with serum cystatin C within the Chronic Renal Insufficiency Cohort (CRIC) Study GFR subcohort. The solid line is the linear regression line and the dotted line represents the lowess fit. The scatterplots were created in the log scale, but axis labels have been converted back to the original scale.

Figure 2.
Performance of the final Chronic Renal Insufficiency Cohort (CRIC) Study glomerular filtration rate (GFR) estimating equation refit in the validation dataset by level of estimated GFR.

Table 1

Demographic and clinical characteristics

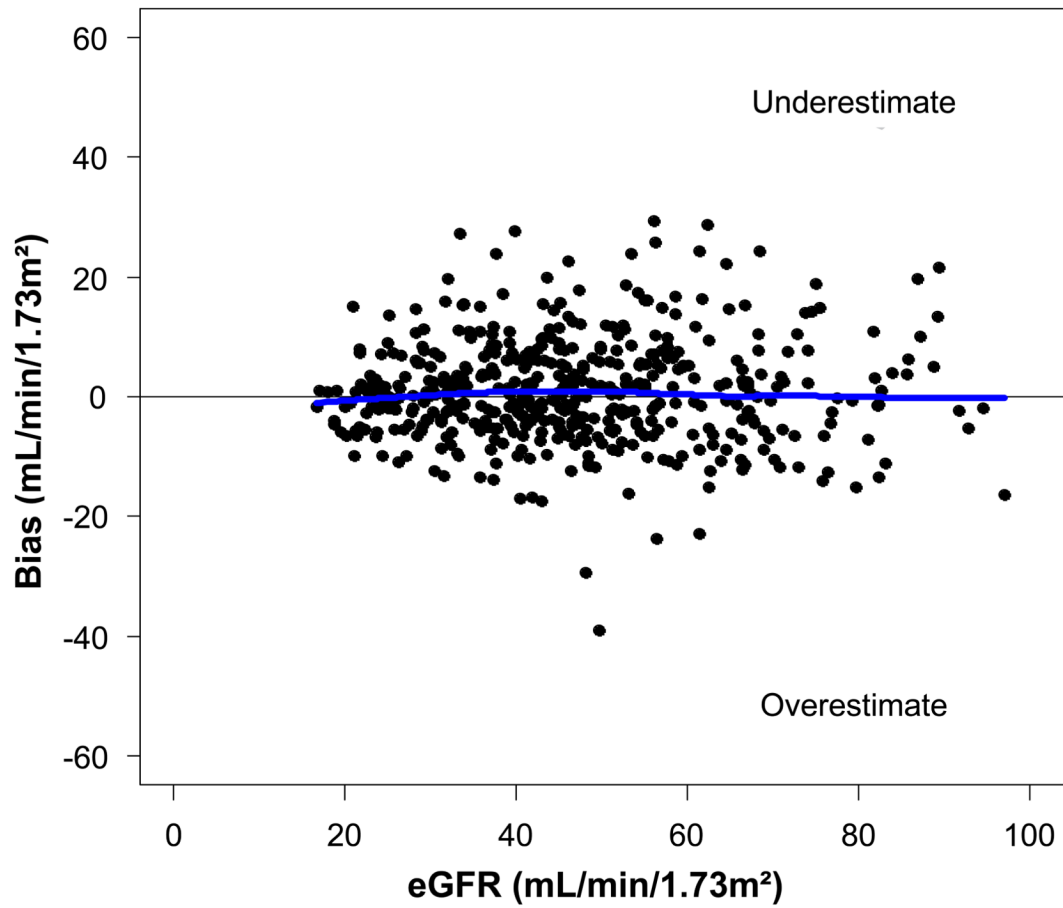| | Entire Cohort (n=3939) | Participants in GFR Subcohort | | P-value |
		Yes (n=1433)	No (n=2506)	
mGFR				
including first clearance period (mL/min/1.73 m2)	-	49.0 ±21.0)	-	-
excluding first clearance period (mL/min/1.73 m2)	-	48.0 ±19.9)	-	-
Age (y)	58.2 ±11.0)	56.0 ±12.3)	59.4 ±10.0)	<0.001
Female gender	1778 (45.1)	628 (43.8)	1150 (45.9)	0.2
Black race	1658 (42.1)	534 (37.3)	1124 (44.9)	<0.001
Hispanic	497 (12.6)	215 (15.0)	282 (11.3)	<0.001
Diabetes present	1907 (48.4)	689 (48.1)	1218 (48.6)	0.8
Height (cm)	168.8 ±9.7)	168.9 ±9.5)	168.8 ±9.8)	0.7
Weight (kg)	91.5 ±23.4)	89.4 ±21.0)	92.8 ±24.6)	<0.001
BMI (kg/m^2)	32.1 ±7.8)	31.3 ±6.9)	32.5 ±8.3)	<0.001
Waist circumference (cm)	105.8 ±17.6)	103.8 ±16.1)	107.0 ±18.3)	<0.001
BIA resistance (ohm)	463.9 ±104.4)	467.9 ±101.3)	461.6 ±106.2)	0.07
BIA reactance (ohm)	54.4 ±26.0)	54.8 ±23.6)	54.1 ±27.2)	0.5
BIA phase angle (degrees)	6.9 ±4.2)	6.8 ±3.7)	6.9 ±4.5)	0.5
Fat-free mass [†] (kg)	60.5 ±15.6)	59.8 ±15.0)	61.0 ±15.9)	0.03
Impedance [†] (ohm)	468.2 ±102.7)	472.2 ±99.9)	465.9 ±104.2)	0.07
Serum creatinine[‡] (mg/dL)	1.74 ±0.58)	1.70 ±0.57)	1.77 ±0.58)	<0.001
Serum cystatin C (mg/L)	1.52 ±0.55)	1.46 ±0.52)	1.55 ±0.56)	<0.001
Serum albumin (g/dL)	3.9 ±0.5)	3.9 ±0.5)	4.0 ±0.5)	<0.001
SUN (mg/dL)	29.6 ±13.6)	29.3 ±13.3)	29.9 ±13.8)	0.2
24-h urine protein (mg/d)	184.3 [73.1-910.0]	210.8 [76.5-1073.1]	171.1 [71.4-839.5]	0.01
24-h urine creatinine (mg/dL)	70.8 ±36.9)	68.0 ±35.0)	72.4 ±37.9)	<0.001
24-h urine creatinine (g/d)	1.3 ±0.6)	1.4 ±0.6)	1.3 ±0.6)	0.002
UPCR (mg/g) [*]	152.5 [57.5-777.8]	160.8 [59.1-941.4]	145.9 [56.3-724.0]	0.08
24-h urine albumin (mg/d)	64.3 [10.3-558.7]	84.1 [10.8-646.7]	57.8 [9.9-508.6]	0.004
24-h urine urea nitrogen (g/d)	8.6 ±4.4)	8.8 ±4.3)	8.5 ±4.5)	0.08
Plasma glucose (mg/dL)	115.4 ±51.7)	112.7 ±48.8)	117.0 ±53.2)	0.01
Total plasma homocysteine (mg/L)	2.0 ±0.8)	2.0 ±0.8)	2.1 ±0.9)	<0.001
hsCRP (mg/L)	2.6 [1.1-6.5]	2.2 [0.9-5.2]	2.8 [1.1-7.1]	<0.001
BNP (pg/mL)	40.6 [17.0–96.0]	36.7 [15.4-83.6]	43.1 [18.0-101.9]	<0.001
Fibrinogen (mg/dL)	416.9 ±121.1)	403.8 ±118.3)	424.4 ±122.1)	<0.001
Insulin (μU/mL)	16.3 [10.9-25.4]	15.6 [10.5-24.6]	16.5 [11.2-25.9]	0.01
IL-6 (pg/mL)	1.9 [1.2-3.2]	1.7 [1.1-2.8]	2.0 [1.2-3.4]	<0.001
TNF-α (pg/mL)	2.2 [1.5-3.2]	2.2 [1.5-3.3]	2.2 [1.5-3.2]	0.6

	Entire Cohort (n=3939)	Participants in GFR Subcohort		P-value
		Yes (n=1433)	No (n=2506)	
IL-1ra (pg/ml)	715.7 [390-1551]	715.0 [370-1508]	717.1 [397-1569]	0.1
Urine NGAL (ng/ml)	14.9 [5.0-35.4]	13.9 [5.0-32.2]	15.5 [5.0-38.0]	0.004
Creatinine clearance (mL/min)	58.2 ±30.5)	61.2 ±31.1)	56.5 ±30.0)	<0.001
HOMA-IR	6.6 ±8.7)	6.3 ±7.7)	6.8 ±9.2)	0.1
SI-HOMA	0.2 [0.1-0.4]	0.3 [0.1-0.4]	0.2 [0.1-0.4]	0.02
Body surface area (m^2)	2.06 ±0.29)	2.04 ±0.27)	2.07 ±0.30)	<0.001

Note: unless otherwise indicated, values for continuous variables given as mean ± SD or median [25th-75th percentile], while values for categorical variables given as number (percentage).

BIA – bioelectrical impedance analysis; BMI – body mass index; BNP – brain natriuretic protein; GFR – glomerular filtration rate; HOMA-IR – homeostasis model assessment – insulin resistance; hsCRP – high-sensitivity C-reactive protein; IL-1ra – interleukin 1 receptor antagonist; IL-6 – interleukin 6; mGFR – measured GFR; NGAL – neutrophil gelatinase-associated lipocalin; SI-HOMA – homeostasis model assessment – insulin sensitivity; Sun, serum urea nitrogen; TNF-α - tumor necrosis factor α; UPCR, urine protein-creatinine ratio.

*
Determined from 24-h urine sample

†
From BIA data

‡
Traceable to isotope dilution mass spectrometry.

Note: Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; creatinine clearance in mL/min to mL/s, ×0.01667; serum albumin in g/dL to g/L, ×10; SUN in mg/dL to mmol/L, ×0.357; plasma glucose in g/dL to mmol/L, ×0.05551; insulin in μU/mL to pmol/L, ×6.00.

Table 2

Associations of demographic and clinical characteristics with measured glomerular filtration rate (GFR) in the Chronic Renal Insufficiency Cohort (CRIC) Study GFR subcohort

	Relationship with Measured GFR			
	Unadjusted		Adjusted for Age, Race and Gender	
	PE* (95% CI)	P-value	PE* (95% CI)	P-value
Age (per 10 years)	-0.108 (-0.155, -0.060)	<0.001	-0.108 (-0.155, -0.060)	<0.001
Female (versus male)	-0.028 (-0.146, 0.091)	0.7	-0.023 (-0.141, 0.094)	0.7
Black (versus non-black)	-0.144 (-0.265, -0.023)	0.02	-0.143 (-0.263, -0.023)	0.02
Hispanic (versus non-Hispanic)	-0.332 (-0.527, -0.137)	0.001	-0.456 (-0.656, -0.257)	<0.001
Diabetes (versus no diabetes)	0.111 (0.053, 0.169)	<0.001	-0.331 (-0.448, -0.214)	<0.001
Height (cm)	-0.055 (-0.115, 0.004)	0.07	0.168 (0.090, 0.246)	<0.001
Weight (kg)	-0.332 (-0.527, -0.137)	<0.001	-0.05 (-0.113, 0.013)	0.1
BMI (kg/m^2)	-0.123 (-0.183, -0.064)	<0.001	-0.107 (-0.167, -0.046)	0.001
Waist circumference (cm)	-0.138 (-0.196, -0.080)	<0.001	-0.113 (-0.173, -0.054)	<0.001
BIA resistance (ohm)	0.058 (-0.003, 0.118)	0.06	0.076 (0.007, 0.146)	0.03
Log (BIA reactance, ohm)	0.218 (0.157, 0.279)	<0.001	0.207 (0.142, 0.271)	<0.001
Log (BIA phase angle, degrees)	0.205 (0.139, 0.271)	<0.001	0.206 (0.133, 0.28)	<0.001
Fat-free mass† (kg)	-0.007 (-0.066, 0.052)	0.8	-0.021 (-0.099, 0.057)	0.6
Impedance† (ohm)	0.058 (-0.001, 0.117)	0.06	0.076 (0.008, 0.144)	0.03
Log (serum creatinine‡, mg/dL)	-0.736 (-0.776, -0.697)	<0.001	-0.9 (-0.936, -0.865)	<0.001
Log (serum cystatin C, mg/L)	-0.837 (-0.869, -0.806)	<0.001	-0.838 (-0.869, -0.807)	<0.001
Serum albumin (g/dL)	0.288 (0.230, 0.347)	<0.001	0.305 (0.247, 0.363)	<0.001
Serum urea nitrogen (mg/dL)	-0.623 (-0.670, -0.577)	<0.001	-0.633 (-0.679, -0.587)	<0.001
Log (24-hour urine protein, mg/d)	-0.323 (-0.380, -0.266)	<0.001	-0.393 (-0.451, -0.335)	<0.001
24-hour urine creatinine (mg/dL)	0.207 (0.149, 0.265)	<0.001	0.234 (0.174, 0.295)	<0.001
Log (24-hour urine creatinine, g/d)	0.214 (0.158, 0.271)	<0.001	0.246 (0.184, 0.309)	<0.001
24-hour urine protein:creatinine ratio (mg/g)	-0.298 (-0.359, -0.237)	<0.001	-0.331 (-0.391, -0.270)	<0.001
Log (24-hour urine albumin, mg/d)	-0.309 (-0.367, -0.251)	<0.001	-0.371 (-0.430, -0.312)	<0.001
Log (24-hour urine urea nitrogen, g/d)	0.199 (0.141, 0.258)	<0.001	0.195 (0.135, 0.255)	<0.001
Plasma glucose (mg/dL)	-0.056 (-0.116, 0.004)	0.07	-0.049 (-0.109, 0.010)	0.1
Log (total plasma homocysteine, mg/L)	-0.488 (-0.540, -0.436)	<0.001	-0.499 (-0.552, -0.445)	<0.001
Log (hsCRP, mg/L)	-0.099 (-0.159, -0.040)	0.001	-0.082 (-0.142, -0.022)	0.008
Log (BNP, pg/mL)	-0.312 (-0.369, -0.256)	<0.001	-0.313 (-0.373, -0.254)	<0.001
Log (fibrinogen, mg/dL)	-0.178 (-0.237, -0.119)	<0.001	-0.16 (-0.219, -0.101)	<0.001
Log (insulin, μU/mL)	-0.114 (-0.174, -0.055)	<0.001	-0.104 (-0.164, -0.045)	0.001
Log (IL-6, pg/mL)	-0.261 (-0.318, -0.204)	<0.001	-0.24 (-0.299, -0.182)	<0.001
Log (TNF-α, pg/mL)	-0.327 (-0.384, -0.269)	<0.001	-0.327 (-0.384, -0.270)	<0.001

	Relationship with Measured GFR			
	Unadjusted		Adjusted for Age, Race and Gender	
	PE* (95% CI)	P-value	PE* (95% CI)	P-value
Log (IL-1ra, pg/mL)	-0.166 (-0.225, -0.107)	<0.001	-0.174 (-0.233, -0.115)	<0.001
Log (urine NGAL, ng/mL)	-0.361 (-0.418, -0.304)	<0.001	-0.411 (-0.470, -0.352)	<0.001
Log (creatinine clearance, mL/min)	0.611 (0.565, 0.657)	<0.001	0.608 (0.562, 0.654)	<0.001
Log (HOMA-IR)	-0.114 (-0.173, -0.055)	<0.001	-0.103 (-0.162, -0.044)	0.001
Log (SI-HOMA)	0.103 (0.047, 0.160)	<0.001	0.085 (0.027, 0.142)	0.004

BIA – bioelectrical impedance analysis; BMI – body mass index; BNP – brain natriuretic protein; CI – confidence interval; GFR – glomerular filtration rate; HOMA-IR – homeostasis model assessment – insulin resistance; hsCRP – C-reactive protein; IL-1ra – interleukin-1 receptor antagonist; IL-6 – interleukin-6; NGAL – neutrophil gelatinase-associated lipocalin; PE – parameter estimate; SI-HOMA – homeostasis model assessment – insulin sensitivity; TNF-α - tumor necrosis factor-α.

*
Parameter estimate represents relative change in measured GFR per one standard deviation increase in predictors unless otherwise specified. Multiplying the parameter estimates by 100 provides approximate percent change;

†From BIA data;

‡Traceable to isotope dilution mass spectrometry.

Table 3

Coefficients and performance of models to estimate GFR in the development dataset from the GFR subcohort

| Model | Regression Coefficient (SE) | | | | | | | Model Performance | |
	SCr	Age	Female Gender	Black Race	SCysC	BIA phase angle	24-h UCr	RMSE (95% CI)	R^2 (95% CI)
1. SCr, age, gender, race	-1.230 (0.026)	-0.059 (0.006)	-0.300 (0.017)	0.096 (0.016)				0.237 (0.223-0.249)	0.696 (0.660-0.729)
2. SCr, age, gender, race, SCysC	-0.598 (0.043)	-0.034 (0.006)	-0.184 (0.016)	0.043 (0.015)	-0.636 (0.037)			0.208 (0.194-0.220)	0.767 (0.737-0.798)
3. SCr, age, gender, race, SCysC, BIA phase angle	-0.604 (0.043)	-0.030 (0.006)	-0.172 (0.016)	0.033 (0.015)	-0.618 (0.037)	0.102 (0.029)		0.206 (0.193-0.219)	0.770 (0.739-0.801)
4. SCr, age, gender, race, SCysC, BIA phase angle, CRIC clinical center,*	-0.578 (0.044)	-0.031 (0.006)	-0.167 (0.017)	0.015 (0.015)	-0.623 (0.038)	0.095 (0.030)		0.204 (0.190-0.216)	0.778 (0.747-0.808)
5. SCr, age, gender, race, SCysC, BIA phase angle, CRIC clinical center, 24-h UCr*	-0.603 (0.046)	-0.028 (0.006)	-0.135 (0.018)	0.007 (0.016)	-0.583 (0.040)	0.066 (0.030)	0.199 (0.034)	0.199 (0.187-0.212)	0.787 (0.757-0.816)

UCr – urine creatinine excretion; BIA – bioelectrical impedance analysis; CI – confidence interval; CRIC – Chronic Renal Insufficiency Cohort; SCysC – serum cystatin C; RMSE – root mean square error; SCr – serum creatinine; SE – standard error; GFR, glomerular filtration rate

*
Coefficients for CRIC clinical centers are not reported.

Table 4

Performance measures for models estimating GFR in the validation dataset from the GFR subcohort

Model	P$_{30}$ (95% CI)	RMSE (95% CI)
1. SCr, age, gender, race	84 (80-87)	0.232 (0.210-0.268)
2. SCr, age, gender, race, SCysC	89 (86-91)	0.207 (0.183-0.242)
3. SCr, age, gender, race, SCysC, BIA phase angle	89 (86-92)	0.206 (0.182-0.241)
4. SCr, age, gender, race, SCysC, BIA phase angle, CRIC clinical center	90 (87-92)	0.205 (0.181-0.241)
5. SCr, age, gender, race, SCysC, BIA phase angle, CRIC clinical center, 24hr UCr	90 (87-92)	0.202 (0.178-0.238)

UCr – urine creatinine excretion; BIA – bioelectrical impedance analysis; CI – confidence interval; CRIC – Chronic Renal Insufficiency Cohort; SCysC – serum cystatin C; P$_{30}$ – percentage of estimated GFR within 30% of measured GFR; RMSE – root mean square error; SCr – serum creatinine; GFR, glomerular filtration rate

Table 5

Performance of the CRIC Study GFR estimating equation in the validation dataset by subgroup

	No.	Median Difference*	Median % Difference*	P$_{30}$ (95% CI)	RMSE (95% CI)
Age					
<45 y	102	1 [-4, 7]	2 [-9, 12]	95 (89-99)	0.170 (0.140-0.207)
45-<60 y	163	0 [-6, 7]	0 [-14, 11]	87 (81-92)	0.212 (0.182-0.249)
60 y	219	1 [-4, 6]	1 [-10, 11]	87 (82-91)	0.215 (0.175-0.279)
Gender					
Female	217	0 [-5, 7]	1 [-13, 11]	86 (81-90)	0.234 (0.192-0.300)
Male	267	0 [-4, 6]	1 [-10, 12]	90 (87-94)	0.181 (0.162-0.199)
Race					
Black	196	1 [-4, 7]	3 [-10, 14]	84 (78-89)	0.223 (0.198-0.248)
Non-black	288	0 [-5, 5]	-1 [-12, 10]	92 (88-95)	0.194 (0.156-0.253)
Ethnicity					
Hispanic	67	-2 [-8, 2]	-5 [-21, 5]	86 (76-94)	0.216 (0.152-0.297)
Non-Hispanic	417	1 [-5, 7]	2 [-10, 12]	89 (86-92)	0.205 (0.180-0.242)
Diabetes					
Yes	224	0 [-5, 6]	1 [-15, 12]	83 (77-88)	0.240 (0.199-0.303)
No	260	1 [-4, 7]	1 [-10, 11]	93 (90-96)	0.172 (0.154-0.191)
BMI					
<25 kg/m^2	89	-2 [-6, 2]	-4 [-12, 5]	93 (86-98)	0.143 (0.116-0.178)
25-<30 kg/m^2	143	2 [-4, 7]	4 [-9, 14]	94 (89-97)	0.174 (0.154-0.197)
30 kg/m^2	252	0 [-5, 7]	1 [-13, 12]	84 (79-88)	0.239 (0.203-0.295)
24-h urine creatinine					
<2.08 g/d	174	-1 [-6, 4]	-4 [-17, 8]	85 (79-90)	0.235 (0.179-0.314)
2.08-<2.55 g/d	160	0 [-4, 6]	-1 [-10, 11]	88 (82-92)	0.192 (0.167-0.220)
2.55 g/d	150	2 [-3, 8]	4 [-6, 13]	93 (88-96)	0.188 (0.162-0.218)
hsCRP					
<1.22 mg/L	162	-1 [-5, 3]	-3 [-12, 7]	92 (88-96)	0.168 (0.145-0.190)

	No.	Median Difference[*]	Median % Difference[*]	P$_{30}$ (95% CI)	RMSE (95% CI)
1.22–<3.82 mg/L	170	1 [-4, 7]	2 [-12, 12]	89 (84-94)	0.221 (0.173-0.299)
3.82 mg/L	152	1 [-4, 7]	2 [-9, 14]	84 (76-89)	0.225 (0.192-0.263)
eGFR					
<45 mL/min/1.73m^2	233	0 [-4, 6]	1 [-13, 14]	82 (77-87)	0.221 (0.200-0.242)
45 mL/min/1.73m^2	251	0 [-6, 7]	1 [-11, 11]	94 (91-97)	0.190 (0.148-0.256)

Abbreviations and definitions: BMI – body mass index; CI – confidence interval; CRIC – Chronic Renal Insufficiency Cohort; eGFR – estimated glomerular filtration rate; GFR, glomerular filtration rate; hsCRP – high-sensitivity C-reactive protein; P30 – percentage of eGFR within 30% of mGFR; RMSE – root mean square error; Median difference: median mGFR – eGFR; Median % difference: median ((mGFR – eGFR)/mGFR); mGFR, measured glomerular filtration rate.

[*]
25th and 75th percentile shown in parentheses.