Glomerular Diseases

Research Article

Glomerular Dis 2024;4:119–128
DOI: 10.1159/000539353

Received: January 22, 2024
Accepted: April 29, 2024
Published online: May 16, 2024

Evaluation of Biomarker-Based Glomerular Filtration Rate Estimating Equations in Glomerular Disease

Antara Mondal[a, b] Christina Kobe[c] Laura H. Mariani[c] Jarcy Zee[a, d]

[a]Division of Biostatistics, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, PA, USA; [b]Department of Biomedical and Health Informatics, Data Science and Biostatistics Unit, The Children's Hospital of Philadelphia, Philadelphia, PA, USA; [c]Division of Nephrology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA; [d]Department of Pediatrics, Children's Hospital of Philadelphia Research Institute, Philadelphia, PA, USA

Keywords
Serum creatinine · Cystatin-C · Glomerular filtration rate estimation · Agreement

Abstract
Introduction: Glomerular filtration rate (GFR) is typically estimated with equations that use biomarkers such as serum creatinine and/or cystatin-C. The impact of these different biomarkers on GFR estimates in glomerular disease patients is unclear. In this study, we compared the different GFR estimating equations in the Cure Glomerulonephropathy (CureGN) cohort of children and adults with glomerular disease. ***Methods:*** All available cystatin-C measurements from CureGN study participants were matched to same-day serum creatinine measurements to estimate GFR. To explore the strength of agreement between eGFR values obtained from the "Under 25" (U25) and Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equations, we used intraclass correlation coefficients. Multivariable linear mixed effects models were used to determine which factors were independently associated with differences in eGFR values. ***Results:*** A total of 928 cystatin-C measurements were matched to same-day serum creatinine measurements from N = 332 CureGN study participants (58% male, 69% White/Caucasian, 20% Black/African American). Among 628 measurements collected while study participants were under 25 years old, there was moderate agreement (0.731) in serum creatinine versus cystatin-C U25 equations. Models showed that higher eGFR values were associated with larger differences between the two equations (p < 0.001). Among 253 measurements collected while study participants were at least 18 years old, there was excellent agreement (0.891–0.978) among CKD-Epi equations using serum creatinine alone, cystatin-C alone, or the combination of both. Younger age was associated with larger differences between CKD-Epi equations (p = 0.06 to p = 0.016). ***Conclusion:*** Excellent agreement between CKD-Epi equations indicates continued use of serum creatinine alone for GFR estimation could be appropriate for adults. In contrast, only moderate agreement between U25 equations indicates a need for more frequent measurement of cystatin-C among children and young adults, especially as eGFR increases.

karger@karger.com
www.karger.com/gdz

Correspondence to:
Jarcy Zee, jarcy.zee@pennmedicine.upenn.edu

Introduction

Accurate measurement of glomerular filtration rate (GFR) is critical to track kidney function and disease progression over time. In the absence of measured GFR, it can be estimated by equations that utilize biomarkers including serum creatinine (SCr) and/or cystatin-C (CysC), alongside demographic factors like age and sex. The "Under 25" (U25) equations have been developed for children and young adults under 25 years of age [1], while the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equations were recently updated for adults 18 and over [2].

The Kidney Disease Improving Global Outcome (KDIGO) guidelines recommend the use of SCr for initial evaluation of eGFR and additional tests based on other markers like CysC for confirmatory testing when SCr-based eGFR could be inaccurate [3]. For example, KDIGO suggests using CysC in patients with a GFR of 45–59 mL/min/1.73 m^2 and no markers of kidney disease to confirm a CKD diagnosis. Clinically, nephrologists measure CysC when a patient has very high or low muscle mass [4]. Since the U25 and CKD-Epi equations were developed among patients with CKD, a relatively small proportion of glomerular disease patients were included. In glomerular disease patients, eGFR is often higher at disease onset than that of patients with non-glomerular CKD, particularly in patients with hyperfiltration. However, CysC is often unavailable due to higher associated costs and lack of routine measurement compared to creatinine. Thus, most studies in patients with glomerular disease still rely solely on SCr-based estimates of GFR.

This study compared the creatinine based, CysC based, and combination GFR estimating equations in the Cure Glomerulonephropathy (CureGN) glomerular disease cohort to evaluate the differences in GFR estimates and whether certain subgroups were more likely to have greater differences. A large difference in results would indicate the need to potentially invest in CysC collection, while smaller differences could justify the continued use of SCr alone for clinical research studies.

Methods

Study Sample

CureGN is an ongoing multicenter prospective observational cohort study of adult and pediatric patients with biopsy-proven minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, or immunoglobulin A nephropathy (IgAN) [5]. Participants were enrolled within 5 years of their first clinically indicated kidney biopsy at participating clinical sites throughout the USA, Canada, Italy, and Poland. All CureGN participants provided written informed consent (adults) or assent with parental written consent (children). The current study consisted of secondary data analysis of existing, de-identified data from CureGN and included all CureGN participants with at least one CysC measurement before chronic dialysis or transplant. This study was determined to be not human subject research by the Children's Hospital of Philadelphia Institutional Review Board (IRB #22-020363).

Data Collection and Definitions

Demographics such as age, sex, and race were collected at the time of study enrollment. Race was self-reported, or reported by parents of the children, and reporting race in CureGN was mandated by the US National Institutes of Health, consistent with the Inclusion of Women, Minorities, and Children policy. Clinical data were collected during follow-up visits every 4–6 months to record serum CysC, SCr, urinary protein-creatinine ratio (UPCR), urinary albumin-creatinine ratio (UACR), urinalysis (UA) dipstick results, and steroid medication use. UPCR and UACR were obtained from a first morning void, random spot urine, or an aliquot of a 24-h urine collection, depending on availability. The central CureGN laboratory used a Randox RX Daytona chemistry analyzer to measure serum and urine creatinine, using the Jaffe method, and urine protein using a colorimetric method. When central measurements were not available, measurements from clinical site laboratories were used. CysC measurements above 10 mg/L were considered errors and excluded.

For the current study, CysC measurements were matched to SCr measurements from the same date whenever available. Any matched pairs of measurements where the absolute value difference between CysC and SCr was greater than or equal to 3 were also considered errors and removed. Among the remaining measurements, eGFR was calculated based on the age- and sex-based U25 equations and CKD-Epi equations according to study participant age at the time of biomarker measurement (Table 1). Two U25 equations (CysC only and SCr only) were compared, and three CKD-Epi equations (CysC only, SCr only, and CysC and SCr combined) were compared. Study participants between the ages of 18 and 25 at the time of biomarker measurements contributed to both U25 and CKD-Epi comparisons. Multiple biomarker measurements over time within the same participant were included in analyses to increase sample size and precision of estimates, as described below.

A binary indicator for steroid use at the time of CysC measurement was created by determining whether the CysC measurement date was within the start and stop dates of any oral or intravenous steroid medications recorded in the CureGN database. Disease activity was determined based on the closest urine protein measurement (UPCR, UACR, or UA dipstick) within 90 days of the CysC measurement for all study participants and both urine protein and urine blood (UA dipstick) for IgAN participants. A hierarchy was implemented if measurements were collected on the same day, with UPCR taking precedence if available, then UACR, then UA dipstick results. For each CysC measurement date, disease activity was then categorized into 4 categories: minimal (UPCR <0.3 g/g or UACR <0.3 g/g or UA protein negative/trace or UA blood

Glomerular Dis 2024;4:119–128
DOI: 10.1159/000539353

Table 1. SCr and CysC-based U25 and CKD-Epi equations for estimating GFR

U25 (for children and adults under 25 years old)		
SCr only	$eGFR = K \times \frac{height}{SCr}$	$K = \begin{cases} 39.0 \times 1.008^{age-12} & \text{if male ages 1 to } < 12 \\ 39.0 \times 1.045^{age-12} & \text{if male ages 12 to } < 18 \\ 50.8 & \text{if male ages 18 to 25} \\ 36.1 \times 1.008^{age-12} & \text{if female ages 1 to } < 12 \\ 36.1 \times 1.023^{age-12} & \text{if female ages 12 to } < 18 \\ 41.4 & \text{if female ages 18 to 25} \end{cases}$
CysC only	$eGFR = K \times \frac{1}{CysC}$	$K = \begin{cases} 87.2 \times 1.011^{age-15} & \text{if male ages 1 to } < 15 \\ 87.2 \times 0.960^{age-15} & \text{if male ages 15 to } < 18 \\ 77.1 & \text{if male ages 18 to 25} \\ 79.9 \times 1.004^{age-12} & \text{if female ages 1 to } < 12 \\ 79.9 \times 0.974^{age-12} & \text{if female ages 12 to } < 18 \\ 68.3 & \text{if female ages 18 to 25} \end{cases}$
CKD-Epi (for adults aged 18 years or older)		
SCr only	$eGFR = 142 \times \min\left(\frac{SCr}{0.7}, 1\right)^{-0.241} \times \max\left(\frac{SCr}{0.7}, 1\right)^{-1.2} \times 0.9938^{age} \times 1.012$ if female,	
	$eGFR = 142 \times \min\left(\frac{SCr}{0.9}, 1\right)^{-0.302} \times \max\left(\frac{SCr}{0.9}, 1\right)^{-1.2} \times 0.9938^{age}$ if male	
CysC only	$eGFR = 133 \times \min\left(\frac{CysC}{0.8}, 1\right)^{-0.499} \times \max\left(\frac{CysC}{0.8}, 1\right)^{-1.328} \times 0.9962^{age} \times 0.932$ if female,	
	$eGFR = 133 \times \min\left(\frac{CysC}{0.8}, 1\right)^{-0.499} \times \max\left(\frac{CysC}{0.8}, 1\right)^{-1.328} \times 0.9962^{age}$ if male	
SCr + CysC	$eGFR = 135 \times \min\left(\frac{SCr}{0.7}, 1\right)^{-0.219} \times \max\left(\frac{SCr}{0.7}, 1\right)^{-0.544} \min\left(\frac{CysC}{0.8}, 1\right)^{-0.323} \times \max\left(\frac{CysC}{0.8}, 1\right)^{-0.778} \times 0.9961^{age} \times 0.963$ if female,	
	$eGFR = 135 \times \min\left(\frac{SCr}{0.9}, 1\right)^{-0.144} \times \max\left(\frac{SCr}{0.9}, 1\right)^{-0.544} \min\left(\frac{CysC}{0.8}, 1\right)^{-0.323} \times \max\left(\frac{CysC}{0.8}, 1\right)^{-0.778} \times 0.9961^{age}$ if male	

Age is measured in years, height in m, SCr in mg/dL, and CysC in mg/L. U25 equations from Pierce et al. [1]; CKD-Epi equations from Inker et al. [2].

Table 2. Demographics and clinical characteristics at enrollment of CureGN study participants with any pre-dialysis/transplant cystatin measurements during follow-up versus those without CysC (subject level)

Characteristic	Has CysC, *N* = 332	No CysC, *N* = 2,391
Sex, *n* (%)		
Female	138 (42)	1,032 (43)
Male	194 (58)	1,359 (57)
Age at enrollment, years		
Median (IQR)	15 (9, 24)	35 (16, 54)
Race, *n* (%)		
Asian	14 (4.4)	210 (9.1)
Black/African American	64 (20)	362 (16)
Native American	6 (1.9)	13 (0.6)
Pacific Islander	2 (0.6)	7 (0.3)
White/Caucasian	218 (69)	1,643 (72)
Multiracial	13 (4.1)	61 (2.7)
Unknown	15	95
Diagnosis, *n* (%)		
MCD	82 (25)	517 (23)
FSGS	89 (27)	568 (25)
MN	46 (14)	533 (24)
IgAN	115 (35)	623 (28)
eGFR at enrollment		
Median (IQR)	88 (65, 109)	82 (51, 103)
Unknown	36	426
UPCR at enrollment		
Median (IQR)	0.9 (0.2, 4.2)	1.2 (0.2, 3.8)
Unknown	64	612

Values are *n* (%) or median (interquartile range, IQR). MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy.

negative/trace for IgAN), mild (UPCR ≥0.3 and <1 g/g or UACR ≥0.3 and <1 g/g or UA protein 1+ or UA blood 1+ for IgAN), moderate (UPCR ≥1 and <3 g/g or UACR ≥1 and <3 g/g or UA protein 2+ or UA blood 2+ for IgAN), and severe (UPCR ≥3 g/g or UACR ≥3 g/g or UA protein ≥3+ or UA blood 3+ for IgAN). Sensitivity analyses were also conducted by requiring that the disease activity marker was within 14 days of CysC measurement. A binary indicator was created to represent provider preference or other unmeasured factors that would result in many CysC measurements within an individual, i.e., 5+ versus <5 measurements over study follow-up.

Statistical Analysis

Summary statistics were used to describe and compare demographics and clinical characteristics at the time of CureGN study enrollment among study participants who did versus did not have any CysC measurements collected before dialysis or transplant. Summary statistics were also used to describe disease activity, steroid use, and age at the time of CysC measurements. Since measured GFR was not available to determine accuracy of SCr- and CysC-based estimating equations, we used intraclass correlation coefficients (ICCs) to measure the strength of agreement between eGFR values calculated by different equations among CysC measurements successfully matched to SCr measurements on the same date. ICCs were also calculated within subgroups by disease diagnosis, SCr-based eGFR value, number of CysC measurements, disease activity, and steroid use. ICCs are preferable to standard correlation coefficients for assessing agreement because they not only estimate the magnitude of the relationship between values but also account for the bias (difference) between values. Since there are no consensus guidelines for interpretation of ICC values, we considered values less than 0.40 to reflect poor agreement, 0.40 up to 0.60 as fair, 0.60 up to 0.80 as moderate, and 0.80 or above as excellent. For comparison, Pearson's correlation coefficients were similarly calculated to estimate associations between eGFR equations. To visualize the differences in eGFR values, Bland-Altman plots and scatterplots were generated. Bland-Altman plots compare the mean of two (e.g., SCr based vs. CysC based) eGFR values to the absolute or relative difference between the two values. Plots also include middle, upper, and lower shaded regions to show the means and confidence intervals of the (absolute or relative) bias, upper limit of agreement, and lower limit of agreement, respectively.

Finally, multivariable linear mixed effects models were used to determine whether any factors had an independent association with the absolute value difference in eGFR values between equations. Models included a random intercept for each study participant to account for multiple measurements within an individual. Age, sex, disease diagnosis, SCr-based eGFR value, number of CysC measurements, disease activity, and steroid use

Table 3. Participant characteristics during CysC measurements (N = 944 measurements from 332 study participants)

	N = 944
Disease activity closest to CysC collection (within 90 days)[a], *n* (%)	
Minimal	301 (32)
Mild	166 (18)
Moderate	195 (21)
Severe	223 (24)
Unknown (those outside of 90 days)	59 (6)
Steroid use during CysC collection, *n* (%)	
Yes	147 (16)
No	777 (82)
Unknown[b]	20 (2)
Age at CysC collection	
Median (IQR)	16 (12, 20)
Range	2, 78
Age at CysC collection ≤18 (pediatric), *n* (%)	639 (68)
Age at CysC collection <25, *n* (%)	780 (83)

Values are *n* (%) or median (interquartile range, IQR). [a]Disease activity closest to CysC collection thresholds: Minimal: UPCR <0.3 or UACR <0.3 or Prot Neg/trace or Blood Neg/trace (IgA). Mild: UPCR [0.3, 1) or UACR [0.3, 1) or Prot 1+ or Blood 1+ (IgA). Moderate: UPCR [0.3, 1) or UACR [0.3, 1) or Prot 1+ or Blood 1+ (IgA). Severe: UPCR ≥3 or UACR ≥3 or Prot ≥3+ or Blood 3+ (IgA). [b]These CysC measurements were from study participants who had steroid medications recorded, but all records had unknown start and stop dates.

were included as covariates. All statistical analyses were conducted using R software, version 4.2.3 (R Development Core Team, Vienna).

Results

A total of N = 332 CureGN study participants had 944 CysC measurements collected before dialysis or transplant. Demographic and clinical characteristics of those who had CysC measurements compared to CureGN participants who did not (N = 2,391) are provided in Table 2. Study participants with CysC measurements were younger and had higher eGFRs at enrollment compared to those without CysC collected. Additionally, those with CysC measurements had a slightly higher proportion of Black/African American patients, a higher proportion of IgAN participants, and fewer membranous nephropathy participants.

CysC measurements were somewhat evenly distributed across disease activity groups, with slightly more collected during periods of minimal disease activity (Table 3). The majority of CysC measurements were collected when study participants were younger, with 83% collected under the age of 25 and 68% collected under age 18. Most (82%) CysC measurements were collected at a time when the participant was not on steroid medication. Out of 944 total CysC measurements available, 16 measurements were removed for subsequent comparison analyses due to large absolute value differences over 3 between CysC and SCr, resulting in a final sample of 928 with a matching SCr measurement on the same date.

Comparisons between U25 Equations

There were 628 CysC measurements with a matching SCr collected while study participants were under 25 and that were used to compare U25 equations. The ICC between the SCr-based U25 equation and CysC-based U25 equation was 0.731 (Table 4). Figure 1 (left panel) shows many differences >10 mL/min/1.73 m^2 or >25% mL/min/1.73 m^2 and greater absolute differences at higher mean eGFR levels. ICC values were lower for study participants with minimal change disease and IgAN, higher eGFR values, and lower disease activity (Table 3; online suppl. online suppl. Fig. 1–3; for all online suppl. material, see https://doi.org/10.1159/000539353). Similar patterns were observed with Pearson's correlation coefficient (online suppl. Table 1; online suppl. Fig. 5–9). ICC values were slightly lower when participants were on steroids compared with not being on steroids (Table 3;

Table 4. ICC between eGFR values using SCr and CysC-based U25 (for ages <25) and CKD-Epi (for ages ≥18) equations (*N* = 928)

	N	U25	*N*	CKD-Epi		
		SCr versus CysC		SCr versus CysC	SCr versus SCr+CysC	CysC versus SCr+CysC
Overall	628	0.731	253	0.891	0.962	0.978
Disease diagnosis						
MCD	167	0.68	25	0.911	0.974	0.978
FSGS	144	0.802	73	0.891	0.957	0.983
MN	62	0.889	65	0.912	0.969	0.98
IgAN	255	0.614	90	0.848	0.949	0.969
SCr eGFR value						
<60	125	0.582	123	0.682	0.885	0.929
60 to <90	203	0.216	69	0.454	0.705	0.915
90 to <120	208	0.09	53	0.559	0.744	0.931
120+	92	0.144	8	0.256	0.464	0.888
No. CysCs						
5+	313	0.719	86	0.885	0.96	0.978
<5	315	0.725	167	0.895	0.964	0.979
Disease activity						
Minimal	254	0.44	70	0.844	0.947	0.965
Mild	128	0.698	48	0.76	0.914	0.953
Moderate	123	0.733	59	0.915	0.971	0.984
Severe	123	0.855	76	0.907	0.967	0.982
Steroid use						
No	502	0.743	231	0.898	0.966	0.979
Yes	113	0.707	14	0.908	0.967	0.984

SCr, serum creatinine; CysC, cystatin-C; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; IgAN, immunoglobulin A nephropathy; minimal, UPCR <0.3 or UACR <0.3 or Prot Neg/trace or Blood Neg/trace (IgA); mild, UPCR [0.3, 1) or UACR [0.3, 1) or Prot 1+ or Blood 1+ (IgA); moderate, UPCR [0.3, 1) or UACR [0.3, 1) or Prot 1+ or Blood 1+ (IgA); severe, UPCR ≥3 or UACR ≥3 or Prot ≥3+ or Blood 3+ (IgA); U25, equation used in subjects under 25 years; CKD-Epi, equation used in subjects 18 years and older.

online suppl. Fig. 4). Oral steroid dose information was available for 97 observations, which had a median (interquartile range) dose of 10 (5–30) mg. ICC values among those with steroid dose ≥10 mg versus <10 mg were 0.791 and 0.63, respectively.

Higher eGFR values were associated with larger differences between the U25 SCr and CysC equations ($p < 0.001$) after controlling for age, sex, disease diagnosis, number of cystatin collections, disease activity, and steroid use (Table 5). Younger age was also associated with larger differences between equations ($p < 0.001$).

Comparisons between CKD-Epi Equations

There were 253 CysC measurements with a matching SCr collected while study participants were over age 18 and that were used to compare CKD-Epi equations. The overall ICC comparing CKD-Epi equations based on SCr only versus CysC only was 0.891 (Table 4; Fig. 1 right panel). Agreement was slightly lower for study participants with IgAN and with mild disease activity (Table 4; online suppl. Fig. 1, 3). The ICC when eGFR was over 120 mL/min/1.73 m^2 was low, but there was a very small sample size for this subgroup (Table 4; online suppl. Fig. 2). ICCs were similar by steroid use (Table 4; online suppl. Fig. 4), but there were too few observations to compare ICCs across steroid doses. When comparing either of these equations to the CKD-Epi combination equation with both SCr and CysC, agreement was much higher overall (ICCs of 0.962 and 0.978) and within all subgroups (ICCs >0.90) except when eGFR was over 60 mL/min/1.73 m^2. Similar patterns were observed with Pearson's correlation coefficient (online suppl. Table 1; online suppl. Fig. 5–9).

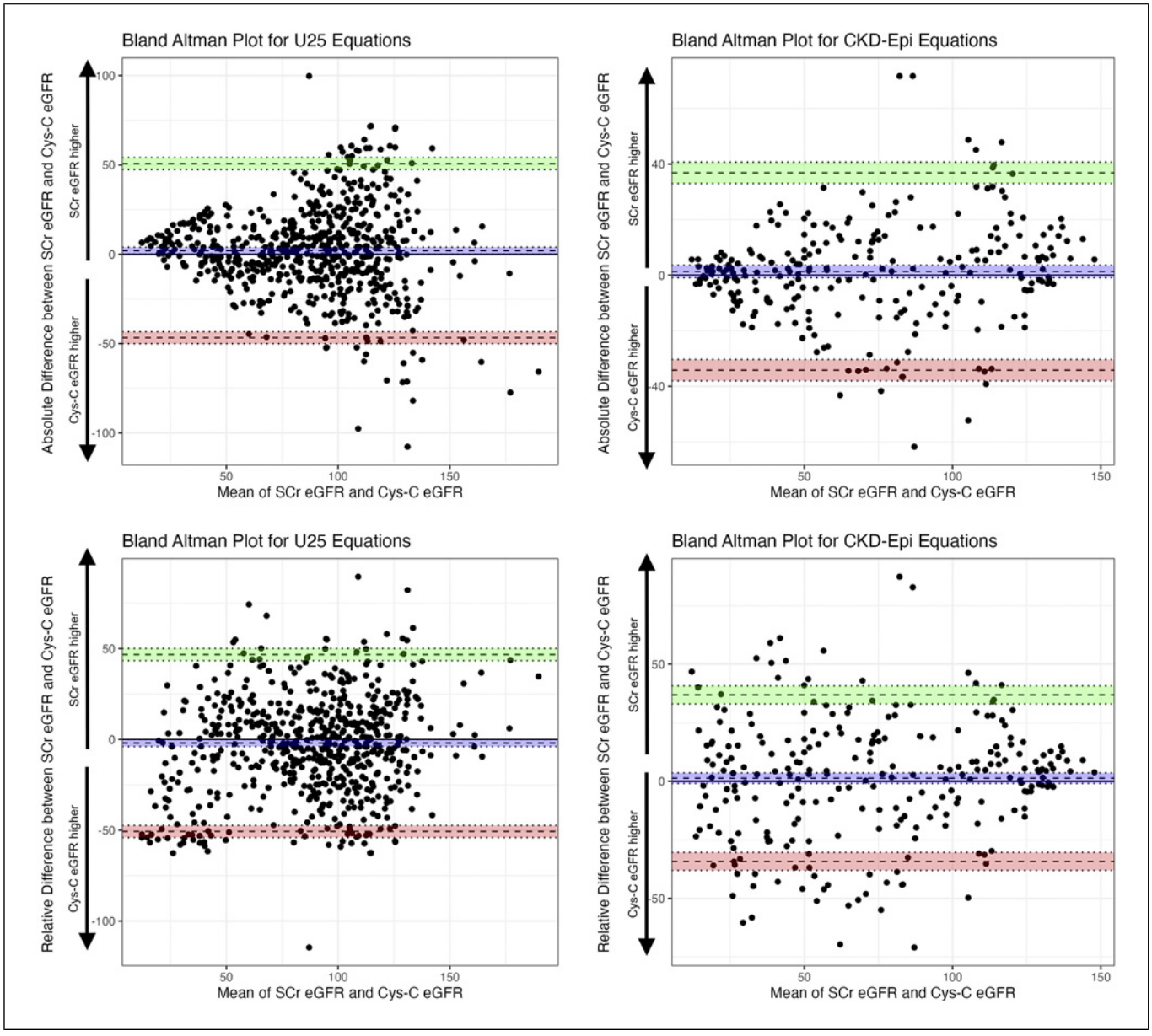

Fig. 1. Bland-Altman plots comparing eGFR values between SCr and CysC-based U25 and CKD-Epi equations. The middle (blue), upper (green), and lower (red) shaded regions show the means and confidence intervals of the (absolute or relative) bias, upper limit of agreement, and lower limit of agreement between SCr and CysC eGFR values, respectively. The top row shows absolute differences in eGFR, and bottom row shows relative differences in eGFR.

Model results (Table 5) indicated that eGFR had a significant adjusted association with the difference in equations when comparing the SCr-only equation to the combination equation (p = 0.003). In all three CKD-Epi equation comparisons, younger age was associated with larger differences between equations.

Discussion

Overall, there was excellent agreement between eGFR values calculated using different CKD-Epi equations and moderate agreement between different U25 equations. Agreement was poor in some subgroups, including

Table 5. Adjusted associations between clinical factors and differences in eGFR across estimating equations

	U25			CKD-Epi								
	SCr versus CysC			SCr versus CysC			SCr versus SCr+CysC			CysC versus SCr+CysC		
	estimate	SE	*p* value	estimate	SE	*p* value	estimate	SE	*p* value	estimate	SE	*p* value
Age	−0.30	0.21	<0.001	−0.13	0.07	0.01	−0.07	0.04	0.006	−0.06	0.03	0.016
Male sex	−2.27	2.09	0.37	−0.35	2.23	0.89	0.20	1.24	0.89	−0.96	1.02	0.41
Disease diagnosis (ref: MCD)			0.06			0.33			0.16			0.311
FSGS	−0.94	2.82		−1.98	3.75		−1.21	2.08		−0.40	1.72	
MN	−6.03	3.74		2.10	3.77		1.28	2.09		1.51	1.73	
IgAN	−3.09	2.47		2.03	3.55		1.11	1.97		1.14	1.63	
SCr eGFR value, per 10mL/min/1.73^2	0.17	0.02	<0.001	0.02	0.04	0.49	0.04	0.02	0.03	0.009	0.02	0.553
5+ CysC collections	0.18	2.21	0.97	0.04	2.88	0.96	−0.90	1.61	0.56	0.69	1.31	0.68
Disease activity (ref: minimal)			0.78			0.23			0.26			0.0.23
Mild	−1.51	1.73		2.69	2.28		1.20	1.23		1.42	1.08	
Moderate	0.19	1.83		−2.01	2.43		−1.10	1.32		−0.82	1.15	
Severe	0.02	1.91		0.32	2.40		0.44	1.30		−0.33	1.13	
Steroid use	0.54	1.70	0.75	−1.06	3.34	0.75	−0.51	1.82	0.78	−0.75	1.58	0.64

Ref, reference; SE, standard error; SCr, serum creatinine; CysC, cystatin-C; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; IgAN, immunoglobulin A nephropathy; minimal, UPCR <0.3 or UACR <0.3 or Prot Neg/trace or Blood Neg/trace (IgA); mild, UPCR [0.3, 1) or UACR [0.3, 1) or Prot 1+ or Blood 1+ (IgA); moderate, UPCR [0.3, 1) or UACR [0.3, 1) or Prot 1+ or Blood 1+ (IgA); severe, UPCR ≥3 or UACR ≥3 or Prot ≥3+ or Blood 3+ (IgA).

individuals with higher eGFRs and among children and young adults with minimal disease activity when using the U25 equations. Only age and eGFR value had significant adjusted associations with the differences between the U25 SCr and CysC equations.

Younger age and high eGFR were associated with larger discrepancies between SCr and CysC equations, which may be related to more inaccurate estimation of GFR in these patients. This finding supports the KDIGO recommendation to confirm eGFR values using markers like CysC when SCr-based estimates of GFR are high. Since glomerular disease patients often have eGFRs that are higher than those of the CKD patients in which the equations were developed, the need for CysC would likely be more frequent in this population. Although agreement was low between U25 equations among study participants with minimal disease activity, disease activity was not significantly associated with the difference in eGFR values after controlling for other factors. Since disease activity is inversely correlated with eGFR, the low agreement with minimal disease activity was likely driven by having higher eGFR values.

Results were similar whether or not participants were using steroids at the time of biomarker measurement. The use of corticosteroids is known to increase SCr due to their catabolic effects, whereas less is known about the effect of steroids on CysC. However, evidence from transplant patients indicates that steroids may increase CysC production and similarly lead to an underestimation of GFR [6, 7]. It may also be the case that a difference exists but our study was not powered to detect a difference, or that a difference only exists when steroid dose is high. In fact, we did find lower ICC between U25 equations among those taking higher doses of steroids. Future, larger studies with sufficient steroid dose data would be needed to fully investigate this hypothesis.

We expected that SCr- and CysC-based eGFR values would have very high correlation. While CKD-Epi equations resulted in eGFR values that were more similar, the comparison between U25 equations showed lower agreement. Given that the U25 equations were previously shown to have less bias in estimating measured GFR [1] compared with the bias of the CKD-Epi equations [2], our results suggest that one or both of the U25 equations may be less accurate in glomerular disease patients than in the largely non-glomerular disease CKD populations in which they were developed. Future studies that can assess

the accuracy of GFR estimating equations in glomerular disease patients would be valuable to confirm this hypothesis, especially as it relates to age. In the meantime, our results may indicate greater need for CysC to confirm eGFR values when using the U25 equations in children and young adults with glomerular disease.

There are a few limitations of this study worth noting. First, measured GFR was not available to determine which equations were most accurate for estimating GFR in this cohort. We therefore relied on agreement measures and an assumption from CKD literature that equations based on CysC were similarly or more accurate. Second, since CysC was only available in a subset of CureGN patients whose providers ordered that laboratory measure, there may be selection bias in the study sample. For example, if those with CysC were patients for whom providers already had suspicion of inaccurate SCr-based eGFRs, our results may represent underestimates of agreement within the full CureGN cohort. Lastly, steroid dose was largely unaccounted for in this analysis and effects on creatinine may vary based on dose and duration of therapy.

Despite these limitations, this study presents the first comparison of different biomarker-based GFR equations in a glomerular disease cohort of both children and adults. Since eGFR is widely used to assess kidney function and to define clinical outcomes in both research studies and clinical practice, discrepancies in GFR estimation based on different biomarkers could alter study results and decision-making in clinical care. In fact, a recent study demonstrated that larger discrepancies between SCr- and CysC-based eGFRs were associated with higher risks of adverse health outcomes [8]. Since we found only moderate agreement in CysC and SCr equations when using the U25 equations in children and young adults and among those with high eGFRs, there is a need for more frequent measurement of CysC in these research participants.

Acknowledgments

CureGN collaborators are listed in online supplementary material.

Statement of Ethics

This study was determined to be not human subject research by the Children's Hospital of Philadelphia Institutional Review Board (IRB #22-020363). This study consisted of secondary data analysis of existing, de-identified data from CureGN. All participants enrolled in the CureGN study provided written informed consent (adults) or assent with parental written consent (children).

Conflict of Interest Statement

Dr. Mariani has received consulting funds from Chinook Therapeutics, Travere Therapeutics, and Calliditas Therapeutics and honoraria from HCPLive. Other authors do not have anything to disclose.

Funding Sources

The current study did not receive funding by any external sponsor. Funding for the CureGN consortium, from which the data for the current study were extracted, is provided by U24DK100845 (formerly UM1DK100845), U01DK100846 (formerly UM1DK100846), U01DK100876 (formerly UM1DK100876), U01DK100866 (formerly UM1DK100866), and U01DK100867 (formerly UM1DK100867) from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Patient recruitment for CureGN is supported by NephCure Kidney International.

Author Contributions

L.H.M. and J.Z. conceptualized and designed the study and provided supervision. A.M. and J.Z. conducted data analysis and drafted the manuscript. A.M., C.K., L.H.M., and J.Z. interpreted analysis results, reviewed the manuscript, and approved the final version.

Data Availability Statement

The data in this study were obtained from the Cure Glomerulonephropathy (CureGN) network where data sharing requires ancillary study approval and a data use agreement. The dataset may be requested from the CureGN Data Coordinating Center (DCC), https://www.dev-curegn.org/.

References

1 Pierce CB, Muñoz A, Ng DK, Warady BA, Furth SL, Schwartz GJ. Age- and sex-dependent clinical equations to estimate glomerular filtration rates in children and young adults with chronic kidney disease. Kidney Int. 2021;99(4):948–56. https://doi.org/10.1016/j.kint.2020.10.047

2 Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737–49. https://doi.org/10.1056/NEJMoa2102953

3 Kidney Disease Improving Global Outcomes KDIGO Glomerular Diseases Work Group, Adler SG, Barratt J. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100(4S):S1–S276. https://doi.org/10.1016/j.kint.2021.05.021

4 Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. Am J Kidney Dis. 2013;62(3):595–603. https://doi.org/10.1053/j.ajkd.2013.03.027

5 Mariani LH, Bomback AS, Canetta PA, Flessner MF, Helmuth M, Hladunewich MA, et al. CureGN study rationale, design, and methods: establishing a large prospective observational study of glomerular disease. Am J Kidney Dis. 2019;73(2):218–29. https://doi.org/10.1053/j.ajkd.2018.07.020
6 Risch L, Herklotz R, Blumberg A, Huber AR. Effects of glucocorticoid immunosuppression on serum cystatin C concentrations in renal transplant patients. Clin Chem. 2001;47(11):2055–9. https://doi.org/10.1093/clinchem/47.11.2055
7 Bökenkamp A, van Wijk JAE, Lentze MJ, Stoffel-Wagner B. Effect of corticosteroid therapy on serum cystatin C and β2-microglobulin concentrations. Clin Chem. 2002;48(7):1123–6. https://doi.org/10.1093/clinchem/48.7.1123
8 Farrington DK, Surapaneni A, Matsushita K, Seegmiller JC, Coresh J, Grams ME. Discrepancies between cystatin C–based and creatinine-based eGFR. Clin J Am Soc Nephrol. 2023;18(9):1143–52. https://doi.org/10.2215/CJN.0000000000000217