Circulation: Heart Failure

ORIGINAL ARTICLE

Performance of Creatinine and Cystatin C-Based Equations to Estimate Glomerular Filtration Rate Among Patients With Heart Failure

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BACKGROUND: The performance of estimated glomerular filtration rate (eGFR) among patients with heart failure (HF) may be worse than in the general population due to a higher prevalence of confounding factors affecting creatinine and cystatin C. Studies in this area are scarce and not stratified by type of HF. We evaluated the performance of current creatinine and cystatin C equations (eGFR creatinine-based equation [eGFRcr], eGFR serum cystatin C-based, and eGFR creatinine-cystatin C equation) compared with measured GFR (mGFR) among patients with HF stratified by ejection fraction.

METHODS: We pulled data on Mayo Clinic patients with an mGFR performed for clinical indications from 2011 to 2023, with serum creatinine and cystatin C measured within 7 days and an echocardiogram performed up to 1 year before the mGFR date. HF was identified by the presence of *International Classification of Diseases* codes within 1 year before the mGFR and subgrouped into ejection fraction (EF) ≥50% (HFEF ≥50%, n=182) or <50% (HFEF<50%, n=115) and compared with no-HF controls (n=1871). CKD-EPI eGFRcr, eGFR serum cystatin C-based, and eGFR creatinine-cystatin C equations were calculated, and compared for bias (mGFR minus eGFR) and accuracy (1-P30, proportion of people with ≥30% difference between eGFR and mGFR). CIs were generated by bootstrapping.

RESULTS: The HF groups were characterized by older age, higher proportion of males, more diabetes, higher creatinine, and higher cystatin C than controls. eGFRcr overestimated mGFR to a greater extent in both HF groups as compared with controls, whereas the eGFR serum cystatin C-based equation showed similar underestimation in both HF groups and controls. In the HF groups, cystatin C-based equations were more accurate than eGFRcr particularly within HFEF <50% (1-P30 of 28% and 34% for eGFR serum cystatin C-based and eGFR creatinine-cystatin C equations, respectively, versus 60% for eGFRcr), whereas eGFR creatinine-cystatin C equation was more accurate in controls.

CONCLUSIONS: Among patients with HF, eGFRcr demonstrates inferior performance (more bias and less accuracy) compared with cystatin C-based eGFRs, with this effect being more pronounced in those with HFEF <50%.

Key Words: creatinine ■ cystatin C ■ humans ■ prevalence ■ stroke volume

Accurate assessment of kidney function and diagnosis of chronic kidney disease is essential among patients with heart failure (HF) for accurate drug dosing, assessment of eligibility for treatment and trials, evaluation of risks related to treatment, safety of imaging and procedures, consideration for combined heart-kidney transplant, and prognostication.[1–3] However, precise assessment of kidney function has posed an ongoing challenge for decades. Most commonly, estimation of the glomerular filtration rate (GFR) relies on equations that include demographics and endogenous filtration markers such as creatinine and cystatin C (estimated GFR or eGFR). Current guidelines within the US recommend the use of a creatinine-based equation (eGFRcr) for initial assessment.[4] If there is clinical suspicion this estimate is inaccurate, providers may pursue confirmatory testing

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WHAT IS NEW?

- Large cohort study in a major US health care system showing creatinine-based estimated glomerular filtration rate equations compared with to cystatin C-based estimated glomerular filtration rate perform worse (more bias and less accuracy) in those with heart failure.
- This effect is more pronounced in those with heart failure with reduced ejection fraction as opposed to those with preserved ejection fraction.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Highlights the frequency and magnitude of errors in estimated glomerular filtration rate in patients with heart failure.
- Identifies the combined creatinine-cystatin C, as opposed to creatinine-only equations as the preferred means of estimating glomerular filtration rate in patients with heart failure.

Nonstandard Abbreviations and Acronyms

CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-EPIcr	Chronic Kidney Disease Epidemiology Collaboration creatinine equation
EF	ejection fraction
eGFR	estimated glomerular filtration rate
eGFRcr	estimated glomerular filtration rate creatinine-based equation
eGFRcrcys	estimated glomerular filtration rate creatinine-cystatin C equation
eGFRcys	estimated glomerular filtration rate serum cystatin C-based
EKFC	European Kidney Failure Consortium
HF	heart failure
ICD	International Classification of Diseases
mGFR	measured glomerular filtration rate
NoHF	no HF

with the combined creatinine-cystatin C equation (eGFRcrcys).[4] In situations where accurate assessment of GFR is paramount for clinical decision-making, guidelines recommend obtaining a measured GFR (mGFR) based on urinary clearance or plasma decay of an exogenous filtration marker, considered as gold standard methods. However, clinical use of the combined eGFR equation or mGFR remains low, particularly among nonnephrologists.

Patients with HF may be at increased risk for factors that confound endogenous filtration markers resulting in inaccurate GFR estimation.[5] For instance, sarcopenia, cachexia, and frailty are common in HF and lead to wasting of skeletal muscle, which is the primary source of creatinine, causing overestimation of true GFR with eGFRcr.[6–8] For cystatin C, underestimation of GFR may occur as a function of changes in adipose tissue mass, smoking, thyroid diseases, endogenous and exogenous glucocorticoids,[9] and stress states leading to increased cystatin C production.[8] Currently, only a few studies with small sample sizes have evaluated the performance of various eGFR equations within HF populations.[10–12] In addition, causes of HF are heterogeneous and could be associated with variable effects on creatinine and cystatin C generation. However, no studies to date have examined eGFR versus mGFR among those with reduced versus normal ejection fraction (EF). Moreover, these studies did not evaluate the race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[13] or recent equations that are widely used in Europe and other countries.

Thus, the aim of this study was to assess the performance of the most recent CKD-EPI and European Kidney Failure Consortium (EKFC) equations compared with mGFR in people with HF stratified by HF subtype.

METHODS

This study was approved by the Mayo Clinic IRB (23-002121). Clinical data and laboratory results were extracted from the Mayo Clinic electronic health record. Briefly, we retrieved all patients >18 years old with mGFR obtained for clinical purposes across all Mayo Clinic sites from May 2011 (after creatinine and cystatin C had both been standardized) to September 2023 who also had a transthoracic echocardiogram within 1 year of the mGFR date (n=32 218). Patients were then classified as having HF if there was an encounter with *International Classification of Diseases* (ICD) 9 or ICD10 code for HF (ICD10 I50 and ICD9 428)[14] within 1 year before mGFR (n=2662) and subclassified according to EF as HFEF ≥50% or HFEF<50%. A control group was defined as people without any encounter for HF (NoHF) who also had an echocardiogram within 1 year of mGFR showing EF ≥50% (n=14 096). Patient with a creatinine (Creat cohort, n=14 857, being n=1467 for HFEF ≥50% and n=994 for HFEF <50%) or creatinine and cystatin C (CreatCys cohort, n=2168, being n=182 for HFEF ≥50% and n=115 for HFEF<50%) performed within 7 days of the date of the mGFR and no missing or implausible laboratory, height, or weight values were retained. If multiple mGFRs were obtained, only the first was used. In our institution, mGFRs are typically done in the outpatient setting. Height and weight were available for the same day for 95% of the sample; in those whose same-day height and weight were not available, we used the closest height and weight within 2 weeks of the date of mGFR. Patients on dialysis were excluded. Validation of HF categories was performed via chart review of 30 randomly selected patients (10 from each group) with excellent performance of 100% correct diagnosis and EF for both the HF and NoHF groups. Furthermore, 100% of patients classified as NoHF did not fulfill the Framingham Heart Failure diagnostic criteria,[15]

whereas 95% of those identified as HF did. Figure S1 depicts the flow and criteria used to define the study population.

All laboratory tests were performed in the Mayo Clinic Central Clinical Chemistry Laboratory. Creatinine was measured using a Roche enzymatic creatinase assay standardized to international reference material using a Roche Cobas chemistry analyzer (c701 or c501; Roche Diagnostics, Indianapolis). Cystatin C was measured by an immunoturbidometric assay traceable to an international reference material (European Reference Material). Gentian reagents were used between May 2011 and May 2021, and Roche reagents from May 2021 to September 2023. We have shown previously that the residuals of the regression of cystatin C on mGFR did not change meaningfully after the introduction of the new assay.[16] The following eGFR equations were evaluated: 2021 CKD-EPI creatinine equation,[13] 2012 CKD-EPI cystatin C equation,[17] 2021 CKD-EPI creatinine-cystatin C equation,[13] 2024 EKFC creatinine equation,[18] 2023 EKFC cystatin equation,[19] and the EKFC creatinine-cystatin C equation, which is the average of the 2024 EKFC creatinine equation and the 2023 EKFC cystatin equation. Required demographics were extracted from the electronic health record or from a questionnaire administered at the time of the mGFR test. Diabetes was defined as self-reported diabetes or presence of an ICD code for diabetes (ICD10 E08–E13, ICD9 249 and 250), and transplantation status was defined via a verified medical history or presence of ICD codes for solid and hematologic transplants (except cornea) before mGFR.

mGFR was measured throughout the study period by non-radiolabeled iothalamate urinary clearance following a standardized protocol. Briefly, patients were asked to report for testing early in the day and in a fasting state to minimize diurnal or dietary variations. Iothalamate was administered subcutaneously followed by oral hydration to encourage urine flow, and a urinary catheter was placed in cases of incomplete bladder emptying. Plasma and urine were collected in timed intervals, and iothalamate was quantified by liquid chromatography tandem mass spectrometry at the Mayo Clinic Renal Testing Laboratory.[20] Measured GFR was normalized as mL/min per 1.73 m^2 with body surface area as estimated by the DuBois formula.[21]

Bias was defined as mGFR minus eGFR, and accuracy by 1-P30, that is, the percentage of people with an eGFR that differed from mGFR by ≥30%; root mean square error and CIs by bootstrapping (n=500) were also computed. The McNemar test was used to compare 1-P30% for paired samples. Results were stratified by transplant status. Another analysis used a control group for each HF group matched for key covariates (age, sex, self-reported race, body mass index, diabetes, and transplant status at the date of mGFR, and mGFR below or above 60 mL/min per 1.73 m^2). Propensity score matching using the nearest neighbor was performed at a 1:1 ratio without replacement and a caliper of 0.2 (R package MatchIt). CKD staging was assessed according to the Kidney Disease Improving Global Outcomes classification[22] for mGFR and each eGFR, and expressed as the percent match when staging using mGFR versus each eGFR.

All analyses and plots were performed using RStudio (2023.12.1 version). The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Table 1 contains descriptive data for the Creat and CreatCys cohorts of the 3 groups by HF status: NoHF, HFEF ≥50%, and HFEF <50%. Patients with HFEF ≥50% and HFEF <50% were older, had a higher percentage of male sex, a higher frequency of diabetes, and lower kidney function compared with those with NoHF. There was a high frequency of mGFR obtained posttransplant as part of kidney, bone marrow, and liver transplant recipient care. Most variables were similar between groups, except for mGFR, which was lower in CreatCys compared with Creat, especially among those with HF.

Table 2 contains eGFR performance metrics for the 3 groups in the Creat and CreatCys cohorts. The CKD-EPI creatinine equation (CKD-EPIcr) demonstrated minimal bias in the NoHF groups but overestimation in HFEF ≥50% and HFEF <50% in the 2 cohorts; a similar pattern was observed using the 2024 EKFC creatinine equation. In terms of precision, in the Creat cohort, 1-P30% of 22%, 30%, and 37% were observed with CKD-EPIcr in the NoHF, HFEF ≥50%, and HFEF <50% groups, respectively, and this trend was even more pronounced in the CreatCys cohort (1-P30% of 22%, 36%, and 60% in NoHF, HFEF ≥50%, and HFEF <50%, respectively). When comparing the performance of creatinine and cystatin C equations within the CreatCys cohort, eGFRcr showed the worst performance in the HF groups, with a 1-P30% of 36% in HFEF ≥50% and 60% in HFEF<50% for the CKD-EPIcr (and 36% in HFEF ≥50% and 56% in HFEF <50% with the 2024 EKFC creatinine equation), in comparison to 22% observed in the NoHF group. Conversely, both CKD-EPI and EKFC eGFRcrcys and serum cystatin C-based (eGFRcys) equations performed better than eGFRcr in the HF groups, with eGFRcrcys being the most accurate in HFEF ≥50% and eGFRcys the most accurate in HFEF <50%. Similar trends were observed when comparing the root mean square error between subgroups within each cohort. Figures 1 and 2 show the scatter plots between the mGFR and the CKD-EPI and EKFC equations, respectively, in the CreatCys cohort. Table S1 shows the performance metrics stratified by transplant status, and in both populations the cystatin C-based equations performed better than eGFRcr, with eGFRcr showing larger errors in the HF groups compared with the non-HF group.

As a sensitivity analysis, the performance metrics were also evaluated using a matched control group. Tables S2 and S3 show the descriptive variables before and after matching for each HF group and its matched control in the Creat and CreatCys cohorts, respectively. Tables S4 and S5 depict the performance of eGFR on mGFR in the matched groups in both cohorts. While adjustments did attenuate differences, the performance was still worse in the HF groups, with larger bias and imprecision observed with eGFRcr compared with eGFRcrcys or eGFRcys.

Table 1. Descriptive Data at mGFR Date of the Creat and CreatCys Cohorts

	Creat cohort				CreatCys cohort			
	NoHF	HFEF ≥50%	HFEF <50%		NoHF	HFEF≥50%	HFEF<50%	
	n=12396	n=1467	n=994	*P*	n=1871	n=182	n=115	*P*
Age at mGFR, y; mean, SD	57 (12)	59 (13)	58 (13)	<0.0001	57 (12)	61 (13)	60 (14)	<0.0001
Gender, male; n (%)	7079 (57)	849 (58)	717 (72)	<0.0001	976 (52)	110 (60)	86 (75)	<0.0001
Self-reported race, White; n (%)	10966 (89)	1267 (86)	846 (85)	0.0004	1660 (89)	161 (89)	96 (84)	0.14
Diabetes, n (%)	2890 (23)	787 (54)	400 (40)	<0.0001	376 (20)	120 (66)	49 (43)	<0.0001
Posttransplant status, n (%)	5331 (43)	1020 (70)	275 (28)	<0.0001	616 (33)	91 (50)	32 (28)	<0.0001
BMI, kg/m^2; mean (SD)	28.9 (6.8)	29.2 (6.7)	28.8 (5.9)	0.18	28.5 (5.7)	28.8 (6.2)	28.4 (6.1)	0.78
Creatinine, mg/dL; mean (SD)	1.2 (0.8)	1.6 (0.8)	1.5 (0.7)	<0.0001	1.3 (0.9)	1.8 (0.9)	1.7 (0.8)	<0.0001
Cystatin, mg/L; mean (SD)	…	…	…	…	1.4 (0.7)	2.2 (1.0)	2.0 (0.7)	<0.0001
BSA-adj. mGFR, mL/min per 1.73 m^2; mean (SD)	75 (32)	53 (26)	55 (26)	<0.0001	72 (33)	42 (24)	41 (19)	<0.0001
BSA-unadj. mGFR, mL/min per 1.73; mean (SD)	84 (38)	60 (31)	63 (32)	<0.0001	80 (38)	47 (28)	48 (24)	<0.0001
CKD-EPI creatinine equation, mL/min per 1.73 m^2; mean (SD)	74 (28)	58 (26)	59 (25)	<0.0001	72 (28)	50 (26)	50 (23)	<0.0001
CKD-EPI cystatin C equation, mL/min per 1.73 m^2; mean (SD)	…	…	…	…	68 (33)	36 (22)	38 (18)	<0.0001
CKD-EPI creatinine-cystatin C equation, mL/min per 1.73m^2; mean (SD)	…	…	…	…	71 (31)	42 (23)	43 (19)	<0.0001
EKFC creatinine equation, mL/min per 1.73 m^2; mean (SD)	71 (25)	56 (24)	58 (23.1)	<0.0001	69 (26)	49(24)	49 (22)	<0.0001
EKFC cystatin equation, mL/min per 1.73 m^2; mean (SD)	…	…	…	…	67 (28)	40 (20)	41 (17)	<0.0001
EKFC creatinine-cystatin C equation, mL/min per 1.73 m^2; mean (SD)	…	…	…	…	68 (25)	44 (21)	45 (17)	<0.0001

P values reflect comparisons across groups within each cohort using Kruskal-Wallis and χ^2 tests for continuous and categorical variables, respectively. BMI indicates body mass index; BSA, body surface area; CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; Creat cohort, cohort for which creatinine was available; CreatCys cohort, cohort for which both creatinine and cystatin C were available; EKFC, European Kidney Failure Consortium; HFEF, heart failure with reduced or mildly reduced ejection fraction; HFEF, heart failure with preserved ejection fraction; mGFR, measured glomerular filtration rate; and NoHF, no heart failure.

Table 3 shows the percent concordance of CKD stage for the 3 groups for the Creat and CreatCys cohorts. Overall, the concordance of CKD staging of eGFRs compared with mGFR was lower in the HF groups than in NoHF. Both eGFR CKD-EPI and EKFC were subject to significant misclassification of CKD staging in the HFEF ≥50% and HFEF <50% groups, which was most pronounced in the latter group. Percent concordance for the NoHF, HFEF ≥50%, and HFEF<50% groups was 76%, 59%, and 55% with CKD-EPI and 75%, 60%, and 54% with EKFC, respectively. The eGFRcrcys demonstrated the highest percent concordance in NoHF (79% for both CKD-EPI and EKFC) and HFEF ≥50% (63% and 59% for CKD-EPI and EKFC, respectively), while eGFRcys showed the highest concordance in HFEF <50% (51% and 53% for CKD-EPI and EKFC, respectively). The concordance of eGFRcr in the HFEF <50% group was as low as 29% for both CKD-EPI and EKFC.

DISCUSSION

Our study has 2 main findings. First, bias and accuracy observed in the HFEF ≥50% and HFEF <50% groups with all eGFR equations were generally worse than in our control group with no HF. This reduced accuracy translated into mismatched CKD staging in both HF groups, reaching concordance in staging in only 55% and 29% in the HFEF <50% group for Creat and CreatCys, respectively. This finding might be expected, since the HF population is quite different from the NoHF population due to a higher burden of cardiovascular risk factors (age, sex, diabetes, hypertension, kidney disease, smoking, cardiotoxic exposures) that may affect non-GFR determinants of eGFR. Additional contributors to the non-GFR determinants of eGFR related to HF include changes in metabolism, cachexia, inflammation, and others. Considering that many of these factors are known to interfere with creatinine and cystatin C and their performance in predicting GFR, worse performance in the HF groups was not unexpected. Regardless of the mechanism, our study demonstrates that the performance of eGFR to predict mGFR is worse in the HF population than in the control group without HF. This carries significant clinical implications and identifies those with HF as a high-risk population that may have additional health risks related to inaccuracies in GFR estimation.

Table 2. Performance of CKD-EPI and EKFC eGFR Equations in the Creat and CreatCys Cohorts Stratified by Heart Failure Diagnosis

	Creat cohort			CreatCys cohort		
	NoHF	HFEF ≥50%	HFEF <50%	NoHF	HFEF ≥50%	HFEF<50%
	n=12 396	n=1467	n=994	n=1871	n=182	n=115
Median bias (CI)						
CKD-EPI creatinine equation	0.5 (0.2 to 0.7)	−3.7 (−4.5 to −3)	−4.1 (−5 to −3.2)	0 (−0.6 to 0.8)	−6 (−8.3 to −4.4)	−8.1 (−11.4 to −3.7)
CKD-EPI cystatin C equation	…	…	…	4.3 (3.4 to 5.4)	4.7 (3.6 to 6.3)	2.6 (−0.4 to 4.4)
CKD-EPI creatinine-cystatin C equation	…	…	…	1.1 (0.4 to 1.9)	0.5 (−0.9 to 2)	−1.5 (−3.1 to 1.3)
EKFC creatinine equation	2.7 (2.4 to 3)	−2.2 (−3.2 to −1.3)	−3.7 (−4.9 to −2.5)	1.9 (0.8 to 2.5)	−4.5 (−6.5 to −2.5)	−7.7 (−11.4 to −2.9)
EKFC cystatin equation	…	…	…	3.4 (2.4 to 4.5)	0.9 (−1.2 to 2.7)	−0.9 (−3.6 to 0.4)
EKFC creatinine—cystatin C equation	…	…	…	2.6 (1.9 to 3.2)	−2 (−3.6 to −0.6)	−6.1 (−11.1 to −3.1)
1-P30 (CI)						
CKD-EPI creatinine equation	21.6 (20.8 to 22.3)	30.1 (27.8 to 32.7)	37.4 (34.3 to 40.4)	22.4 (20.7 to 24.3)	36.3 (29.4 to 43.4)	60 (50.9 to 68.7)
CKD-EPI cystatin C equation	…	…	…	24.6 (22.5 to 26.6)	31.9 (25 to 39)	27.8 (20 to 35.7)
CKD-EPI creatinine-cystatin C equation	…	…	…	15.4 (13.8 to 16.9)	25.3 (18.1 to 31.3)	33.9 (25.2 to 42.6)
EKFC creatinine equation	21.3 (20.6 to 22)	27.5 (25.2 to 29.7)	35.8 (33 to 38.7)	21.4 (19.7 to 23.2)	35.7 (28.6 to 41.8)	55.7 (46.1 to 64.3)
EKFC cystatin equation	…	…	…	20.8 (18.9 to 22.7)	30.8 (23.1 to 37.4)	33 (24.3 to 42.6)
EKFC creatinine-cystatin C equation	…	…	…	15.3 (13.6 to 16.9)	29.1 (22 to 35.2)	42.6 (33 to 50.8)
RMSE						
CKD-EPI creatinine equation	19.2	16.8	19	18.2	18.5	22.0
CKD-EPI cystatin C equation	…	…	…	19.2	15.8	13.4
CKD-EPI creatinine-cystatin C equation	…	…	…	16.1	12.9	13.5
EKFC creatinine equation	19.5	15.9	17.9	18.4	17.4	21
EKFC cystatin equation	…	…	…	18.3	14.4	12.8
EKFC creatinine-cystatin C equation	…	…	…	16.5	12.8	14.3

Bias was computed as mGFR-eGFR. Bias and RMSE are expressed as mL/min per 1.73 m^2. McNemar test *P* values for 1-P30 related to paired samples in the CreatCys cohort: NoHF group, *P*<0.0001 for serum creatinine-based eGFR or serum cystatin c-based eGFR compared with eGFRcrcys; HFEF ≥50%, *P*<0.007 and 0.03 for CKD-EPI creatinine equation, and EKFC creatinine equation in comparison to CKD-EPI creatinine-cystatin C equation and EKFC creatinine-cystatin C equation, respectively, and NS for CKD-EPI cystatin C equation and EKFC cystatin equation in comparison to CKD-EPI creatinine-cystatin C equation and EKFC creatinine-cystatin C equation, respectively; HFEF <50%, *P*<0.0001 and 0.003 for CKD-EPI creatinine equation and EKFC creatinine equation in comparison to CKD-EPI creatinine-cystatin C equation and EKFC creatinine-cystatin C equation, respectively; and NS for CKD-EPI cystatin C equation and EKFC cystatin equation in comparison to CKD-EPI creatinine-cystatin C equation and EKFC creatinine-cystatin C equation, respectively. Creat cohort indicates cohort for which creatinine was available; CreatCys cohort, cohort for which both creatinine and cystatin C were available; CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; EKFC, European Kidney Failure Consortium; HFEF, heart failure with reduced ejection fraction; HFEF, heart failure with preserved ejection fraction; mGFR, measured glomerular filtration rate; NoHF, no prior diagnosis of heart failure; P30, proportion of eGFR within 30% of measured GFR; and RMSE, root mean square error.

The second main finding refers to the comparative performance of eGFRs within the HF population. Unlike the no HF controls, eGFRcr had the worst performance in comparison to both eGFRcrcys and eGFRcys within the HF groups. Specifically, eGFRcr demonstrated significant bias and was prone to overestimation of mGFR, as well as poor accuracy. This effect was more pronounced in the HFEF <50% group than in HFEF ≥50%. An eGFR within 30% of mGFR has been considered acceptable for clinical decision-making, and Kidney Disease Improving Global Outcomes recommends eGFR equations should strive for this benchmark in >90% of patients.[22] However, in the CreatCys cohort, use of eGFRcr resulted in up to 60% of people falling outside this metric, with errors above 30%. Even in the Creat cohort (which is less prone to selection bias than the CreatCys cohort), despite root mean square error being similar in the NoHF and HFEF <50% groups, the frequency of larger errors

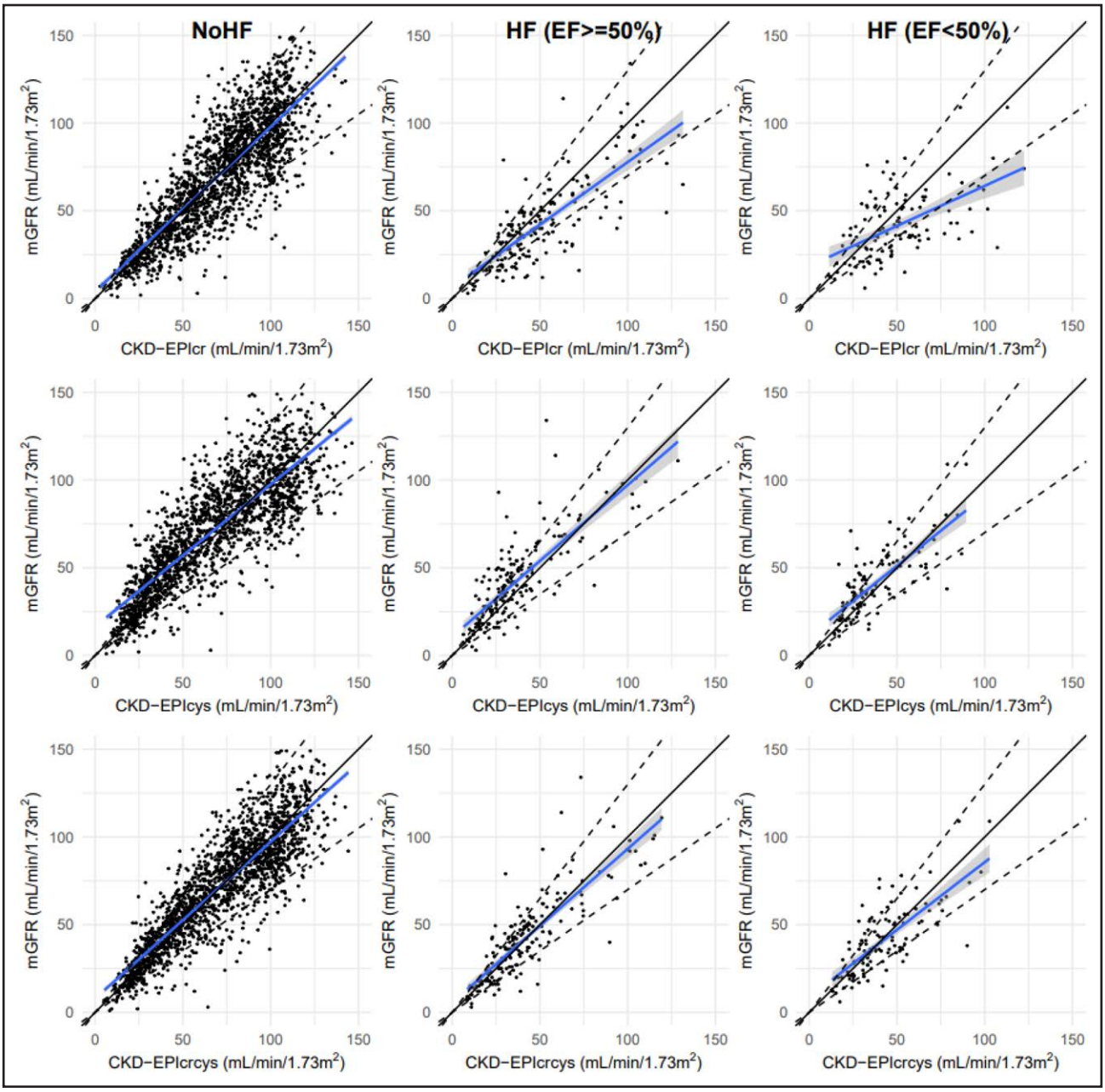

Figure 1. Scatter plots and regression lines of measured glomerular filtration rate (mGFR) and estimated glomerular filtration rate (eGFR) values for the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in the CreatCys cohort. Dots represent values for eGFR and mGFR expressed as mL/min per 1.73 m^2. Dotted line marks upper and lower 30% difference between mGFR and eGFR. Blue line shows the regression lines for the scatter plots and black line shows the reference line (perfect agreement between mGFR and eGFR). CKD-EPIcr indicates Chronic Kidney Disease Epidemiology Collaboration creatinine equation; CKD-EPIcrcys, Chronic Kidney Disease Epidemiology Collaboration creatinine and cystatin C equation; CKD-EPIcys, Chronic Kidney Disease Epidemiology Collaboration cystatin C equation; HFEF, heart failure with preserved ejection fraction; HFEF, heart failure with reduced ejection fraction; and NoHF, no heart failure.

(>30%) went from 22% in the NoHF group, to 30% in the HFEF ≥50% group, and up to 37% in the HFEF <50% group. Possible contributors include sarcopenia, malnutrition, and cachexia which are associated with low muscle mass, the primary determinant of creatinine generation.[11] eGFRcrcys demonstrated the best performance in the HFEF ≥50% group, while eGFRcys had the best performance in the HFEF <50% group followed closely by the eGFRcrcys. Regardless, eGFRcys and eGFRcrcys still show only modest precision with errors >30% occurring in 25% to 42% of patients in the HF groups. Between CKD-EPI and EKFC equations, results were overall similar in numbers and patterns in agreement with prior publications suggesting these equations have found a point of convergence.[23] As there was a likely selection bias regarding which patients had cystatin

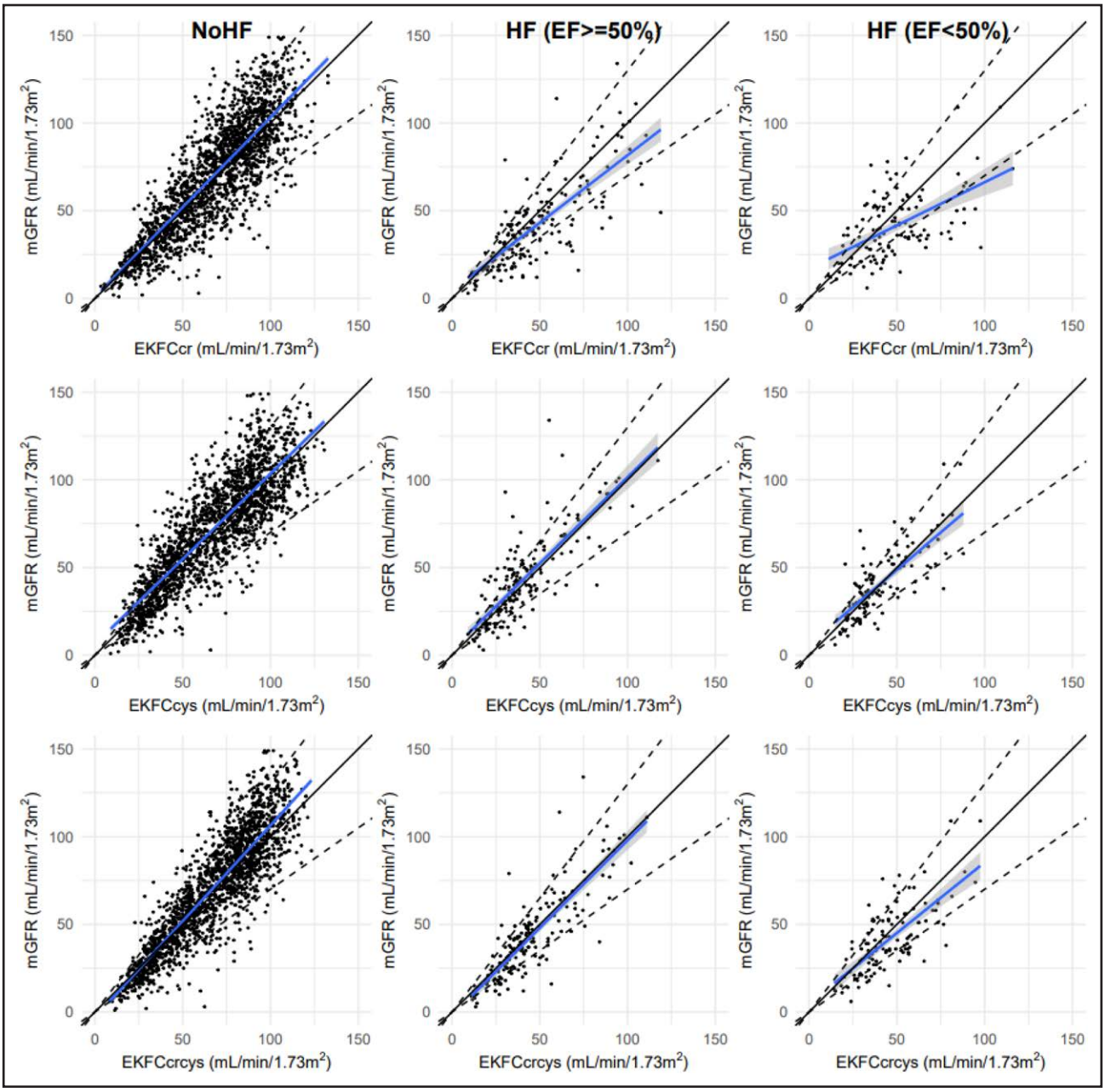

Figure 2. Scatter plots and regression lines of the measured glomerular filtration rate (mGFR) and estimated glomerular filtration rate (eGFR) values for the European Kidney Function Consortium (EKFC) equations in the CreatCys cohort.
Dots represent values for eGFR and mGFR expressed as mL/min per 1.73 m^2. Dotted line marks upper and lower 30% difference between mGFR and eGFR. Blue line shows the regression lines for the scatter plots and black line shows the reference line (perfect agreement between mGFR and eGFR). EKFCcr indicates European Kidney Function Consortium creatinine equation; EKFCcrcys, European Kidney Function Consortium creatinine-cystatin C equation; EKFCcys, European Kidney Function Consortium cystatin equation; HFEF, heart failure with preserved ejection fraction; HFEF, heart failure with reduced ejection fraction; and NoHF, no heart failure.

C testing due to a reason to question the eGFRcr result, it may be reasonable to use eGFRcrcys over eGFRcys in patients with HF. This would also be consistent with the general eGFR literature that suggests eGFRcrcys (but not eGFRcys) is more accurate than eGFRcr.[13,16,24]

Two prior small studies have assessed the performance of eGFRs in HF. Kervella et al[11] evaluated the 2012 CKD-EPI creatinine and cystatin C equations on 66 people with HF as compared with urinary clearance of inulin, showing that the CKD-EPI cystatin C equation had smaller bias but all 3 equations performed poorly, with P30% of 65% for the CKD-EPI cystatin C equation, 52% for Chronic Kidney Disease Epidemiology Collaboration creatinine and cystatin C equation, and 33% for CKD-EPIcr. In another study using plasma clearance of dextran in 50 patients, P30% of 74% for Chronic Kidney Disease Epidemiology Collaboration creatinine and cystatin C equation, 66% for CKD-EPIcr and 56% for

Table 3. Concordance of CKD Stage With eGFR in the Creat and CreatCys Cohorts Stratified by Heart Failure Diagnosis

	Creat cohort			CreatCys cohort		
	NoHF	HFEF ≥50%	HFEF<50%	NoHF	HFEF ≥50%	HFEF<50%
	n=12 396	n=1467	n=994	n=1871	n=182	n=115
CKD-EPI creatinine equation	76.0	59.6	55.3	75.8	53.3	28.7
CKD-EPI cystatin C equation	…	…	…	70.2	51.6	51.3
CKD-EPI creatinine-cystatin C equation	…	…	…	78.5	63.2	46.1
EKFC creatinine equation	75.4	59.7	54.4	74.8	52.2	29.6
EKFC cystatin equation	…	…	…	73.1	58.2	53.0
EKFC creatinine-cystatin C equation	…	…	…	79.4	59.3	40.9

CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; Creat cohort, cohort for which creatinine was available; CreatCys cohort, cohort for which both creatinine and cystatin C were available; EKFC, European Kidney Failure Consortium; HFEF, heart failure with reduced ejection fraction; HFEF, heart failure with preserved ejection fraction; and NoHF, no heart failure.

the CKD-EPI cystatin C equation were described.[12] Our study showed that cystatin C-based equations perform better than eGFRcr in people with HF, although still with moderate precision, and that the overestimation with eGFRcr tends to be more pronounced in those with HFEF <50% as compared with HFEF ≥50%.

Inaccurate estimates of GFR carry significant implications in the care of patients with HF. For example, GFR may affect the decision-making on the use and titration of medications, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitors, and glucagon-like peptides.[25,26] It also impacts drug dosing of some direct oral anticoagulants and low-molecular-weight heparins, with the potential for increased risk of bleeding due to overdosing and ischemic or embolic events due to underdosing.[27] GFR estimation is part of the evaluation for mechanical circulatory support such as left ventricular assist devices,[28,29] and is a crucial parameter to define eligibility for heart-kidney transplantation versus heart transplantation only.[30–33] Per ACC/AHA and Kidney Disease Improving Global Outcomes guidelines, patients at elevated risk for contrast-induced nephropathy should receive adequate periprocedural hydration, and low GFR, particularly in the setting of HF, is considered a significant risk factor.[4,34–37] It is interesting to note that HF trials may use eGFRcr as an inclusion, criterion, which may contribute to heterogeneity in the recruited population and treatment effects.

To the best of our knowledge, this is the single largest investigation into the performance of various eGFR equations in the HF population. Other strengths of our study include the use of standardized assays for serum cystatin C and creatinine, use of urinary iothalamate clearance as mGFR, availability of a control group without HF within the same population, stratification for HF, and the fact that we were able to test modern race-free equations that had not been tested in prior studies.

This study contains several limitations. First, there was likely significant selection bias in the cohorts generated. The HF groups may have overrepresented patients with malignancy, multiple comorbidities, or organ transplants. In addition, selection bias was likely present both in patients who underwent mGFR testing and received echocardiograms, as well as in the subset with cystatin C testing. Notably, mGFR is done by protocol for certain subgroups in our institution (eg, posttransplantation), though we attempted to address this potential bias by stratified analysis by transplant status, which demonstrated similar results regardless of transplant status in the HF patients (but not in the no HF controls). Our population was also predominantly White so our results may not apply to other populations with different demographic characteristics. Notably, the race-free CKD-EPI eGFRcr equation overestimates GFR in White patients and this may have contributed to the overestimation with eGFRcr in HF seen in this study.[38] Since our electronic health record does not include information on medication dispensation and discontinuation systematically, we could not precisely determine if people were on chronic use of steroids at the time of mGFR date. Steroids are known to increase cystatin C production[9] and may cause underestimation of cystatin C-based equations. In addition, we could not assess other medications that can influence creatinine or cystatin C and therefore may confound the performance of eGFRs. Creatinine and cystatin were mostly measured within 1 to 2 days of the mGFR date, but we also allowed labs from up to 1 week of mGFR testing as this introduced minimal variation in the outpatient setting.[16] Our sample sizes for the HFEF ≥50% and HFEF<50% groups were relatively small. Finally, we did not have information on muscle mass, body composition, and frailty, precluding stratified analysis for variables of interest.

CONCLUSIONS

Collectively, the results demonstrate suboptimal performance of eGFRcr in HF populations, with this effect being more pronounced in those with HFEF <50%.

While significant inaccuracy still exists with eGFRcrcys or eGFRcys, our data indicate superior performance of these in comparison to eGFRcr in both HFEF ≥50% and HFEF <50%. These findings support the use of the eGFRcrcys equations in HF, consistent with the general recommendation in the Kidney Disease: Improving Global Outcomes guidelines for use of eGFRcrcys when a more accurate estimation of GFR is needed.

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Disclosures

None.

Supplemental Material

Tables S1–S5
Figure S1

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