The difference between cystatin C- and creatinine-based assessment of kidney function in acute heart failure

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Abstract

Aims Acute heart failure (HF) is associated with muscle mass loss, potentially leading to overestimation of kidney function using serum creatinine-based estimated glomerular filtration rate (eGFR<sub>sCr</sub>). Cystatin C-based eGFR (eGFR<sub>CysC</sub>) is less muscle mass dependent. Changes in the difference between eGFR<sub>CysC</sub> and eGFR<sub>sCr</sub> may reflect muscle mass loss. We investigated the difference between eGFR<sub>CysC</sub> and eGFR<sub>sCr</sub> and its association with clinical outcomes in acute HF patients.

Methods and results A post hoc analysis was performed in 841 patients enrolled in three trials: Diuretic Optimization Strategy Evaluation (DOSE), Renal Optimization Strategies Evaluation (ROSE), and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF). Intra-individual differences between eGFRs were calculated as eGFR<sub>CysC</sub>−eGFR<sub>sCr</sub> at serial time points during HF admission. We investigated associations of (i) change in eGFR<sub>diff</sub> between baseline and day 3 or 4 with readmission-free survival up to day 60; (ii) index hospitalization length of stay (LOS) and readmission with eGFR<sub>diff</sub> at day 60. eGFR<sub>CysC</sub> reclassified 40% of samples to more advanced kidney dysfunction. Median eGFR<sub>diff</sub> was −4 (−11 to 1.5) mL/min/1.73 m<sup>2</sup> at baseline, became more negative during admission and remained significantly different at day 60. The change in eGFR<sub>diff</sub> between baseline and day 3 or 4 was associated with readmission-free survival (adjusted hazard ratio per standard deviation decrease in eGFR<sub>diff</sub>: 1.14, P = 0.035). Longer index hospitalization LOS and readmission were associated with more negative eGFR<sub>diff</sub> at day 60 (both P ≤ 0.026 in adjusted models).

Conclusions In acute HF, a marked difference between eGFR<sub>CysC</sub> and eGFR<sub>sCr</sub> is present at baseline, becomes more pronounced during hospitalization, and is sustained at 60 day follow-up. The change in eGFR<sub>diff</sub> during HF admission and eGFR<sub>diff</sub> at day 60 are associated with clinical outcomes.

Keywords Acute heart failure; Cardiorenal syndrome; Cystatin C; Glomerular filtration rate

Introduction

Kidney dysfunction is a well-known predictor of adverse prognosis among hospitalized heart failure (HF) patients. Serial evaluation of kidney function in this patient population is commonly carried out using serum creatinine (sCr)-based estimates. However, the stability of sCr-based estimated glomerular filtration rate (eGFR) in acute care setting has been challenged, particularly in patients with prolonged hospitali-
Cystatin C (CysC) is an endogenous protease inhibitor that is produced by all nucleated cells and, in contrast to sCr, is less influenced by changes in muscle mass. Among HF patients, CysC may more accurately reflect directly measured kidney function and has demonstrated superior prognostic value when compared with sCr. However, the value of serial CysC measurements for the assessment of kidney function during and following HF hospitalization has not been well described.

Given the different relation of CysC and sCr levels with muscle mass, discrepant estimates of kidney function between these two filtration markers have been investigated as surrogate indicators of sarcopenia. The ratio of sCr to CysC (sCr/CysC) directly correlates with muscle mass in several patient populations. Recently, the difference between CysC- and sCr-eGFR (eGFRdiff) has been investigated in the hypertensive and geriatric populations. Specifically, in both cohorts, a more negative eGFRdiff (sCr-eGFR exceeding CysC-eGFR) was associated with prevalent frailty and increased risk for adverse events. Estimated GFRdiff may dynamically change as a result of progressive muscle mass loss occurring in the setting of critical illness and prolonged hospitalization. Marked discrepancies between CysC- and sCr-eGFR have been recently reported among critically ill patients with COVID-19. In a prior intensive care unit study, CysC- and sCr-eGFR were similar at the time of discharge for patients with short length of stay (LOS), while sCr-eGFR far exceeded CysC-eGFR among patients with longer LOS. Whether eGFRdiff on admission, or longitudinal changes in eGFRdiff, carry prognostic value in hospitalized HF patients remains to be established.

The objective of this post hoc analysis conducted within the National Heart, Lung, and Blood Institute (NHBLI)-sponsored Heart Failure Network is to systematically assess kidney function utilizing CysC- and sCr-eGFR among acute HF patients during and after hospitalization. We hypothesized that the difference between the two estimates of kidney function would widen over the course of the hospitalization, and eGFRdiff would be associated with clinical events, such as mortality, readmissions, and index hospitalization LOS.

Methods

Study population

The study design and the primary results of the Diuretic Optimization Strategy Evaluation (DOSE), Renal Optimization Strategies Evaluation (ROSE), and Cardiorenal Rescue Study in Acute Decompensated HF (CARRESS-HF) have been previously reported. All trials were approved by the institutional review board at each participating site. The datasets used for this study are available through the NHLBI Biologic Specimen and Data Repository Information Coordinating Center.

All three trials were multicentre, randomized studies performed in acute HF patients. Each trial evaluated the efficacy and the effects on kidney function of different approaches to decongestion – loop diuretics (DOSE), low-dose dopamine or nesiritide (ROSE), and ultrafiltration (CARRESS-HF). All three trials excluded patients receiving renal replacement therapy. Additional trial-specific criteria for enrolment included sCr (DOSE and CARRESS-HF excluded patients with sCr > 3 and 3.5 mg/dL, respectively) and sCr-eGFR (inclusion criteria for ROSE: 15 to 60 mL/min/1.73 m²). Notably, patients were eligible for enrolment in CARRESS-HF only in the presence of worsening kidney function, defined as an increase in sCr > 0.3 mg/dL. Among a total of 856 subjects enrolled across the three trials, we included those with at least one concurrent CysC and sCr measurement from core laboratory during the study period (n = 841).

Estimation of glomerular filtration rate

As previously described, CysC and sCr levels were measured at a core laboratory. Estimated GFR was calculated using CysC- (eGFR CysC) and sCr-based (eGFR sCr) Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations and classified according to the categories defined by current guidelines. Values of eGFR were log-transformed to achieve normal distribution. For every concurrent CysC and sCr measurement, eGFRdiff was calculated as the difference between log-transformed eGFR CysC and eGFR sCr, which is equivalent to the log-transformed ratio eGFR CysC/eGFR sCr. Negative values of eGFRdiff correspond to eGFR sCr > eGFR CysC and positive values to eGFR CysC > eGFR sCr. Kidney function assessment was performed at baseline (corresponding to the time of randomization) for all three trials and at day: (i) 3, 7 (or discharge), 60 for DOSE; (ii) 1, 2, 3 for ROSE; (iii) 4, 7 (or discharge), 60 for CARRESS-HF. Notably, baseline kidney function assessment was performed in the first 24 h of index hospitalization for patients enrolled in DOSE and ROSE and at any point during index hospitalization (median 2 days after admission) for patients enrolled in CARRESS-HF.

Baseline characteristics and outcomes

Baseline characteristics were collected at the time of randomization in all patients. Outcomes were available up to 60 day follow-up.
We investigated the association of:

- i) eGFR<sub>diff</sub> (at baseline and day 3 or 4) and change in eGFR<sub>diff</sub> between baseline and day 3 or 4 with a composite of death or readmission for any cause;
- ii) index hospitalization LOS and readmission for any cause with eGFR<sub>diff</sub> at day 60.

**Statistical analysis**

Baseline characteristics were compared using t test or ANOVA for continuous normal-distributed variables, Kruskal–Wallis test for continuous non-normal distributed variables, and χ<sup>2</sup> test for categorical variables. Normal distribution was assessed using histograms, skewness, and kurtosis. Among patients with eGFR<sub>sCr</sub> ≥ 30 mL/min/1.73 m<sup>2</sup> at baseline, logistic regression was used to identify clinical characteristics associated with reclassification to severe kidney dysfunction using eGFR<sub>CysC</sub>. Variables were selected using a stepwise forward selection procedure following the Hosmer–Lemeshow goodness of fit test. Linear mixed models regressed eGFR<sub>CysC</sub>, eGFR<sub>sCr</sub>, and eGFR<sub>diff</sub> longitudinally at different time points. Patients were modelled as random effects to account for within-person correlation of repeated measurements and all models included age, sex, race, and trial. The primary analysis was performed on patients from all 3 trials considering samples collected at baseline, day 3 or 4, day 7 (or discharge), and day 60, when compared with baseline (Supporting Information, Table S2). Across all time points, severe kidney dysfunction (<30 mL/min/1.73 m<sup>2</sup>) was more prevalent when considering eGFR<sub>CysC</sub> (1158 samples, 41%) than eGFR<sub>sCr</sub> (685 samples, 24%, P < 0.001; Figure 1B).

**Results**

**Reclassification of glomerular filtration rate category by cystatin C**

Overall, 2849 concurrent CysC and sCr measurements were available in 841 unique patients. Baseline characteristics stratified by trial are shown in the Supporting Information, Table S1. Compared with eGFR<sub>sCr</sub>, eGFR<sub>CysC</sub> reclassified 1413 (50%) samples to different GFR categories: 1144 (81%) to more advanced and 269 (19%) to less advanced kidney dysfunction. Reclassification to more advanced kidney dysfunction occurred more frequently at day 3 or 4, day 7 (or discharge), and day 60, while the 2nd tertile had higher prevalence of diabetes and while the 3rd tertile had higher prevalence of hypertension and renal function occurred more frequently at day 3 or 4, day 7 (or discharge), and day 60, when compared with baseline (Supporting Information, Table S2).

**Longitudinal changes in the difference between cystatin C- and creatinine-based estimated glomerular filtration rate**

Overall, eGFR<sub>CysC</sub> was significantly lower than eGFR<sub>sCr</sub> at all time points (P < 0.001; Figure 2). Median eGFR<sub>diff</sub> at baseline was −4 (interquartile range [IQR]: −11 to 1.5) mL/min/1.73 m<sup>2</sup>. Baseline characteristics, stratified by tertiles of eGFR<sub>diff</sub> at baseline, are shown in Table 1. Notably, body mass index progressively decreased from the 1st to the 3rd tertile, while the 2nd tertile had higher prevalence of diabetes and kidney dysfunction.

When considering all three trials, eGFR<sub>diff</sub> became more negative from baseline to day 3 or 4 and remained significantly different from baseline up to day 60 (all P < 0.001 vs. baseline; Figure 1C, Figure 2 and Supporting Information, Table S3). There was no significant change in eGFR<sub>diff</sub> between day 3 or 4 and the subsequent time points. A sensitiv-
Figure 1 Overview of the main study findings. (A) Cystatin C may have superior accuracy compared with serum creatinine among patients with prevalent muscle mass loss or sarcopenia (e.g., acute heart failure patients). (B) eGFR_{CysC} reclassifies a large proportion of samples to more advanced kidney dysfunction compared with eGFR_{Scr}. (C) eGFR_{diff} widens during admission, with prolonged hospitalization or readmission associated with more pronounced changes at day 60. A widening in eGFR_{diff} during index hospitalization is independently associated with worse readmission-free survival. In (B), data are presented as number of samples and percentage of total samples (%). In (C), boxes and whiskers represent the interquartile range and the 10th–90th percentile range, respectively. eGFR, estimated glomerular filtration rate; CysC, cystatin C; sCr, serum creatinine; eGFR_{diff}, difference between cystatin C and serum creatinine-based estimated glomerular filtration rate; LOS, length of stay. The illustrations were adapted from Servier Medical Art (https://smart.servier.com/). These are open access images distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Figure 2 Changes over time in eGFR_{CysC}, eGFR_{Scr} and eGFR_{diff}. Boxes and whiskers represent the interquartile range and the 10th–90th percentile range, respectively. eGFR, estimated glomerular filtration rate; CysC, cystatin C; sCr, serum creatinine; eGFR_{diff}, difference between cystatin C- and serum creatinine-based estimated glomerular filtration rate.

ESC Heart Failure 2022; 9: 3139–3148
DOI: 10.1002/ehf2.13975
ity analysis excluding the patients from CARRESS-HF who were enrolled after the initial 24 h of index hospitalization or had ultrafiltration yielded similar results (Supporting Information, Figure S1). In the analysis limited to ROSE, eGFR\textsubscript{diff} showed a progressive widening from the time of admission to day 3 ($P < 0.001$, Figure 3). Results were similar when the analyses were performed using sCr/CysC in lieu of eGFR-

### Table 1 Baseline characteristics stratified by tertiles of eGFR\textsubscript{diff} at baseline

|                      | First tertile –14 [−20 to −11] mL/min/1.73 m\(^2\) | Second tertile –4 [−7 to −3] mL/min/1.73 m\(^2\) | Third tertile 4 [1 to 10] mL/min/1.73 m\(^2\) | P-value |
|----------------------|-------------------------------------------------|-------------------------------------------------|---------------------------------------------|---------|
| Number of patients   |
| Demographic and clinical characteristics |
| Age, years           | 67 ± 13                                         | 68 ± 12                                         | 69 ± 13                                     | 0.11    |
| Female               | 64 (24%)                                        | 79 (29%)                                        | 66 (24%)                                    | 0.32    |
| African–American     | 58 (21%)                                        | 57 (21%)                                        | 66 (24%)                                    | 0.60    |
| Diabetes mellitus    | 157 (58%)                                       | 176 (64%)                                       | 130 (47%)                                   | <0.001  |
| BMI, kg/m\(^2\)      | 33.4 [27.5 to 39.6]                             | 31.6 [26.3 to 38.1]                             | 30.5 [26.3 to 35.4]                         | 0.002   |
| SBP, mmHg            | 118 ± 19                                        | 119 ± 18                                        | 117 ± 18                                    | 0.40    |
| Ischaemic aetiology  | 156 (58%)                                       | 168 (61%)                                       | 153 (56%)                                   | 0.45    |
| LVEF, %              | 46 ± 18                                         | 43 ± 18                                         | 42 ± 18                                     | 0.11    |
| LVEF ≥50%            | 154 (57%)                                       | 144 (52%)                                       | 131 (48%)                                   | 0.11    |
| Trial                | 97 (36%)                                        | 85 (31%)                                        | 111 (41%)                                   | 0.011   |
| ROSE                 | 114 (42%)                                       | 112 (41%)                                       | 119 (43%)                                   | 0.007   |
| CARRESS-HF           | 60 (22%)                                        | 78 (28%)                                        | 44 (16%)                                    | 0.24    |
| Medications          |
| ACEi/ARB             | 147 (54%)                                       | 135 (49%)                                       | 171 (62%)                                   | 0.007   |
| MRA                  | 79 (29%)                                        | 79 (29%)                                        | 64 (23%)                                    | 0.24    |
| Laboratory values    |
| Creatinine, mg/dL    | 1.42 ± 0.41                                     | 1.95 ± 0.61                                     | 1.81 ± 0.63                                 | <0.001  |
| eGFR\textsubscript{Cr}, mL/min/1.73 m\(^2\) | 51 [40 to 63]                                   | 33 [26 to 46]                                   | 38 [27 to 54]                               | <0.001  |
| Cystatin C, mg/L     | 1.85 ± 0.54                                     | 2.09 ± 0.68                                     | 1.51 ± 0.52                                 | <0.001  |
| eGFR\textsubscript{CysC}, mL/min/1.73 m\(^2\) | 34 [26 to 45]                                   | 29 [21 to 41]                                   | 44 [33 to 62]                               | <0.001  |
| BUN, mg/dL           | 43 [24 to 48]                                   | 47 [33 to 66]                                   | 35 [25 to 49]                               | <0.001  |
| Sodium, mEq/L        | 138 ± 4                                         | 138 ± 4                                         | 138 ± 4                                     | 0.53    |
| NT-proBNP, pg/mL     | 4353 [2089 to 9388]                             | 5507 [2371 to 11 664]                           | 4269 [2310 to 9699]                         | 0.16    |

Values are presented as mean ± standard deviation, median [interquartile range], or n (%). BMI, body mass index; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers; MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; sCr, serum creatinine; CysC, cystatin C; BUN, blood urea nitrogen; NT-proBNP, N-terminal pro-brain natriuretic peptide.
quent time points when compared with baseline (Supporting Information, Table S3).

**Association of the difference between cystatin C- and creatinine-based estimated glomerular filtration rate during index hospitalization with readmission-free survival**

Among 720 patients who had samples available at baseline and at day 3 or 4, median eGFR\(_{\text{diff}}\) was \(-4\) (IQR: \(-11\) to \(+1\)) mL/min/1.73 m\(^2\) at baseline and decreased to \(-6\) (IQR: \(-14\) to \(0\)) mL/min/1.73 m\(^2\) at day 3 or 4 (\(P < 0.001\)), resulting in a median change in eGFR\(_{\text{diff}}\) of \(-2\) (IQR: \(-7\) to \(3\)) mL/min/1.73 m\(^2\). Baseline characteristics stratified by tertiles in change of eGFR\(_{\text{diff}}\) are presented in Supporting Information, Table S4. Patients in the 1st tertile of change in eGFR\(_{\text{diff}}\) (indicating wider eGFR\(_{\text{diff}}\) at day 3 or 4 vs. baseline) were younger, more likely to be male and African-American and had lower prevalence of diabetes and kidney dysfunction. In this cohort, the composite outcome occurred in 303 (42%) patients (73 deaths, 263 readmissions for any cause). At baseline and at day 3 or 4, eGFR\(_{\text{diff}}\) had no significant association with readmission-free survival (Table 2). When we considered the change in eGFR\(_{\text{diff}}\) between baseline and day 3 or 4, there was a trend towards an increased risk for the composite outcome with a change in eGFR\(_{\text{diff}}\) towards more negative values (\(P = 0.065\)). After adjustment, this association became significant (hazard ratio per standard deviation decrease: 1.14, \(P = 0.035\); Table 2). The change in sCr/CysC between baseline and day 3 or 4 showed a similar association with the composite outcome (Supporting Information, Table S5).

**Association of index hospitalization length of stay and readmission for any cause with the difference between cystatin C- and creatinine-based estimated glomerular filtration rate at day 60**

The baseline characteristics of the 301 patients from DOSE and CARRESS-HF who had samples available at baseline and Table 2 Association of eGFR\(_{\text{diff}}\) and change in eGFR\(_{\text{diff}}\) with 60 day readmission-free survival

|          | eGFR\(_{\text{diff}}\)_Baseline | eGFR\(_{\text{diff}}\)_Day 3 or 4 | Change in eGFR\(_{\text{diff}}\) between baseline and day 3 or 4 (= eGFR\(_{\text{diff}}\)_day 3 or 4 - eGFR\(_{\text{diff}}\)_baseline) |
|----------|---------------------------------|-------------------------------|------------------------------------------------------------------|
|          | Unadjusted                      | Model 1                       | Model 2 |
| HR (95% CI) per 1-SD decrease Death or readmission for any cause Events | n = 303                       |
|          | Unadjusted                      | Model 1                       | Model 2 |
| eGFR\(_{\text{diff}}\)_Baseline | 1.00 (0.89–1.13) | 1.00 (0.89–1.13) | 0.92 (0.81–1.04) |
|          | \(P\text{-value} = 0.95\)       | \(P\text{-value} = 0.99\)     | \(P\text{-value} = 0.19\) |
| eGFR\(_{\text{diff}}\)_Day 3 or 4 | 1.09 (0.97–1.22) | 1.09 (0.97–1.23) | 1.02 (0.90–1.16) |
|          | \(P\text{-value} = 0.16\)       | \(P\text{-value} = 0.15\)     | \(P\text{-value} = 0.73\) |
|          | \(P\text{-value} = 0.065\)      | \(P\text{-value} = 0.048\)    | \(P\text{-value} = 0.035\) |

HR, hazard ratio; CI, confidence interval; SD, standard deviation; eGFR\(_{\text{diff}}\), Difference between cystatin C- and serum creatinine-based estimated glomerular filtration rate.

aAdjusted for age, sex, race, trial, and baseline serum creatinine-based estimated glomerular filtration rate.

bAdjusted for all the covariates in Model 1 + left ventricular ejection fraction ≥ 50%, systolic blood pressure, use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, N-terminal pro-brain natriuretic peptide, blood urea nitrogen and serum sodium. Six patients were not included in Model 2 due to at least 1 missing variable.

The dependent variable is calculated as the difference between log-transformed eGFR\(_{\text{CysC}}\) and eGFR\(_{\text{Cr}}\). eGFR\(_{\text{diff}}\), difference between cystatin C- and serum creatinine-based estimated glomerular filtration rate; LOS, length of stay. Models 1, 2, and 3 include age, sex, race, trial, and baseline eGFR\(_{\text{diff}}\).

**Table 3 Association of index hospitalization length of stay and readmission for any cause with eGFR\(_{\text{diff}}\) at day 60**

| eGFR\(_{\text{diff}}\) at day 60 dependent variable | Index hospitalization LOS (estimates for each additional day) | \(\geq 1\) Readmission vs. no readmission |
|-----------------------------------------------|---------------------------------------------------------------|----------------------------------------|
| Model                                        | \(\beta\) | \(P\text{-value}\) | \(\beta\) | \(P\text{-value}\) |
| Unadjusted                                    | –0.0073 | <0.001 | –0.067 | 0.052 |
| Unadjusted                                    | –0.0050 | 0.002 | –0.063 | 0.026 |
| Model 1                                       | –0.0050 | 0.002 | –0.065 | 0.026 |
| Model 2                                       | –0.0051 | 0.001 | –0.065 | 0.026 |

The dependent variable is calculated as the difference between log-transformed eGFR\(_{\text{CysC}}\) and eGFR\(_{\text{Cr}}\). eGFR\(_{\text{diff}}\), difference between cystatin C- and serum creatinine-based estimated glomerular filtration rate; LOS, length of stay. Models 1, 2, and 3 include age, sex, race, trial, and baseline eGFR\(_{\text{diff}}\).
at day 60 are shown in Supporting Information, Table S6. Median eGFR_{diff} was \(-4\) (IQR: \(-11\) to +1) mL/min/1.73 m² at baseline and decreased to \(-7\) (IQR: \(-15\) to 0) mL/min/1.73 m² at day 60 (P < 0.001). In this cohort, the median index hospitalization LOS was 6 (IQR: 4 to 9) days and 117 (39%) patients had \(\geq 1\) readmission for any cause. Longer index hospitalization LOS was associated with a more negative eGFR_{diff} at day 60 in univariable and multivariable models (P \(\leq 0.002\), Table 3, Supporting Information, Figure S2A). Of note, the association remained significant in a sensitivity analysis excluding patients with LOS > 20 days (P = 0.008, Supporting Information, Figure S2B). We found a trend for a more negative eGFR_{diff} at day 60 among patients who had \(\geq 1\) readmission for any cause, which became significant after adjustment (Table 3). In a fully adjusted model including both LOS and readmission for any cause, we found that: (i) for every additional 5 days of LOS, there was a 2.5% decrease in eGFR_{diff} at day 60 (P = 0.001); (ii) readmission for any cause was associated with a 6% more negative eGFR_{diff} at day 60 (P = 0.02). Results did not meaningfully differ in models including sCr/CysC in lieu of eGFR_{diff} (Supporting Information, Table S7).

Discussion

The present study has several important findings: (i) the use of eGFR_{CysC} versus eGFR_{sCr} reclassified a large proportion of acute HF patients to more advanced kidney dysfunction; (ii) eGFR_{diff} widened during HF admission and this change was sustained at day 60, particularly in patients with prolonged index hospitalization or readmission; (iii) the change in eGFR_{diff} between baseline and day 3 or 4 was independently associated with a composite of death or readmission for any cause; and (iv) results were similar when sCr/CysC was used in lieu of eGFR_{diff}.

The GFR is the most important measure of kidney function and is reflective of the overall renal reserve, which may partly explain its powerful predictive capacity of HF outcomes. The gold standard for GFR measurement is represented by exogenous markers (e.g. iothalamate). However, these measurements are not practical for routine clinical use. Therefore, endogenous filtration markers are commonly used. Serum creatinine is a product of skeletal muscle creatine metabolism and, as such, represents an imperfect marker for kidney function assessment in conditions characterized by high prevalence of sarcopenia, such as HF. To overcome this limitation, CysC has been suggested as an alternative. CysC is produced by all nucleated cells and is less dependent on muscle mass.

Our study adds to the growing body of literature pointing to the discrepancies in kidney function assessment using the above mentioned renal biomarkers, and suggesting that the use of CysC in the HF population results in markedly lower eGFR when compared with sCr. Recent HF guidelines preferentially recommend the use of sCr as the renal biomarker of choice (Class I, Level C). However, Kidney Disease Improving Global Outcomes guidelines and a position statement from the European Society of Cardiology favour CysC in patients with sarcopenia. Prior research assessing the accuracy of eGFR in the HF population, while limited by single-centre design and relatively small sample size, suggests the superiority of CysC- over sCr-based equations. In HF studies using gold standard methods for GFR measurement (clearance of an exogenous filtration marker), sCr-based equations markedly overestimated kidney function with a mean difference for sCr-based CKD-EPI equation ranging from 15 to 26 mL/min/1.73 m², while CysC-based CKD-EPI provided the closest approximation to the directly measured values. However, this topic remains at the centre of an intense debate. A recent report of 296 HF patients found an association of CysC with muscle mass (although to a lesser extent than sCr), which could potentially bias CysC-based GFR estimates. Indeed, both sCr- and CysC-based equations showed poor accuracy in this study, although the limited precision of creatinine clearance as the reference method to determine kidney function may, at least in part, account for this result.

In agreement with our a priori hypothesis, eGFR_{diff} widened during HF admission. We speculate that changes in eGFR_{diff} might be driven by a decrease in sCr generation secondary to progressive muscle mass loss occurring during HF admission. This interpretation is strengthened by the fact that (i) changes in eGFR_{diff} compatible with muscle wasting were associated with worse readmission-free survival; (ii) prolonged index hospitalization and a subsequent readmission were associated with more negative values of eGFR_{diff} at day 60; and (iii) results were similar when the analysis was performed using sCr/CysC, which has been shown to correlate with muscle mass in prior studies.

An early and progressive muscle mass loss has been described during the first week of critical illness. Ravn et al. showed that sCr-eGFR exceeded CysC-eGFR by 24 mL/min/1.73 m² at the time of discharge from the intensive care unit despite similar estimates at the time of admission. The present results are also in line with our prior findings demonstrating a widening difference between sCr-eGFR and CysC-eGFR during the first month following left ventricular assist device surgery. Notably, in the same report, early post-operative changes in sCr-eGFR correlated with changes in muscle mass as assessed by computed tomography.

Cystatin C levels may rise and peak earlier than sCr in the setting of acute kidney injury. However, the different kinetics of CysC and sCr do not appear to fully explain the change in eGFR_{diff} observed in this study, because eGFR_{diff} did not stabilize during the course of HF admission but rather progressively widened over time.
This study has several important clinical and scientific implications. In acute HF patients, accurate estimation of kidney function is vital in determining appropriate dosing of decongestive therapies and guideline-directed medical therapy. Conventional sCr-based equations may underestimate the prevalence of severe kidney dysfunction and the degree of worsening of kidney function during HF hospitalization and the subsequent follow-up. This may prevent the identification of patients with advanced HF and cardiorenal syndrome and thus delay the initiation of appropriate therapies. Furthermore, clinical trials routinely exclude HF patients with severely reduced sCr-eGFR and incorporate renal endpoints defined by sCr-based estimates. The use of CysC in future trials may improve the selection of participants and possibly provide a more accurate assessment of renal endpoints. Finally, our findings warrant further research investigating eGFRdiff and sCr/CysC as markers of sarcopenia and frailty and thereby prognosis among HF patients.

This study has several limitations. First, in the absence of gold standard measure of GFR, we are unable to definitively conclude which marker provides the most accurate estimate of kidney function in hospitalized HF patients. Similarly, we did not have any objective measures of muscle mass and therefore the relation between changes in eGFRdiff and muscle mass loss, while plausible, remains to be demonstrated. Additionally, we acknowledge that all the eGFR equations used in the present study were derived in patients with stable kidney function and may have limited reliability in hospitalized patients. However, decrease in eGFR has been widely used to define worsening kidney function in acute HF. Moreover, outcomes were available only up to day 60 after HF admission, thus limiting the assessment of long-term prognostic significance of eGFRdiff. Lastly, no adjustment for multiple comparisons was made. Therefore, our study findings should be viewed as hypothesis-generating.

In conclusion, in this post hoc analysis of 3 acute HF trials, CysC led to the reclassification of a large proportion of patients to more advanced kidney dysfunction when compared with sCr-based assessment. During HF admission, eGFRdiff widened, with more pronounced changes at 60 day follow-up among patients with prolonged index hospitalization or readmission. The change in eGFRdiff during HF admission was independently associated with a composite of death or readmission for any cause. Additional studies are warranted to further validate our findings and establish new standards for the assessment of kidney function in acute HF patients.

Acknowledgements

This manuscript was prepared using datasets obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the NHLBI or the study investigators.

Conflict of interest

Y.N. serves as a consultant for Abbott. G.T.S. serves as a consultant for Abbott. N.U. has received research grant support and consultant fees from Abbott and Medtronic. P.C.C. has received research grant support from Abbott and serves as a consultant for the same company. The remaining authors have no conflict of interest to declare.

Funding

This publication was supported from the Lisa and Mark Schwartz Program to Reverse Heart Failure at New York-Presbyterian Hospital/Columbia University.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Changes over time in eGFR$_{\text{CysC}}$, eGFR$_{\text{sCr}}$ and eGFR$_{\text{diff}}$ in a sensitivity analysis excluding those CARRRESS-HF patients who were enrolled after the initial 24 h of index hospitalization or had ultrafiltration.

Figure S2. Association of index hospitalization length of stay with eGFR$_{\text{diff}}$ at day 60. (A) Main analysis. (B) A sensitivity analysis after excluding patients with LOS $> 20$ days.

Table S1. Baseline characteristics stratified by trial.

Table S2. Reclassification of renal function based on eGFR$_{\text{CysC}}$ vs. eGFR$_{\text{sCr}}$ (reference) at individual time points.

Table S3. eGFR$_{\text{CysC}}$, eGFR$_{\text{sCr}}$, eGFR$_{\text{diff}}$, and sCr/CysC ratio across time points.

Table S4. Baseline characteristics stratified by tertiles in change of eGFR$_{\text{diff}}$ between baseline and day 3 or 4.

Table S5. Association of sCr/CysC ratio and change in sCr/ CysC ratio with 60-day readmission-free survival.

Table S6. Baseline characteristics stratified by availability of samples at both baseline and day 60.

Table S7. Association of index hospitalization length of stay and readmission for any cause with sCr/CysC ratio at day 60.

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