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Cystatin C-based CKD-EPI estimated glomerular filtration rate equations as a better strategy for mortality stratification in acute heart failure

A STROBE-compliant prospective observational study

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Abstract

An increasing number of studies outline renal function as an important risk marker for mortality in acute heart failure (AHF). However, routine estimation of glomerular filtration rate (eGFR) based on serum creatinine is imprecise.

This study aims to compare the prognostic impact of CKD-EPI creatinine based equation (eGFRcr), cystatin C based equation (eGFRcyst), and creatinine–cystatin C equation (eGFRcrcyst) for the mortality stratification in AHF.

A total of 354 Patients with AHF were prospectively included between January 2012 and June 2016. Creatinine and cystatin C were measured using the same blood sample tube on admission. We quantified eGFR by the eGFRcr, eGFRcyst, and eGFRcrcyst equations. The continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) were calculated to compare the discriminative prognostic value of different CKD-EPI formula.

After a median follow-up of 35 months, 161 patients (45.5%) died. Reduced eGFRcyst and eGFRcrcyst remained significant association with death after adjustment. eGFRcyst showed the best area under the curve value (0.706) for the prediction of all-cause mortality. Considering mortality reclassification, both eGFRcyst (IDI = 7.3%, $P < .001$; cNRI = 19.6%, $P = .012$) and eGFRcrcyst (IDI = 4.3%, $P < .001$; cNRI = 8.7%, $P = .138$) showed its tendency in improving risk prediction compared to eGFRcr. Compared to eGFRcrcyst showed, eGFRcyst further improved mortality stratification (IDI = 3%, $P = .049$; cNRI = 11.1%, $P = .036$).

In patients with AHF, our study demonstrates the eGFR calculated by CKD-EPI cystatin C-based equation improved the risk stratification of mortality over both creatinine-based and creatinine/cystatin C-based equations.

Abbreviations: ACEI/ARB = angiotension converting enzyme inhibitor/angiotension, ADHF = acute decompensated heart failure, AHF = acute heart failure, AKI = acute kidney injury, AUC = area under curve, CKD = chronic kidney disease, CKD-EPI = chronic kidney disease epidemiology collaboration, CRS = cardiorenal syndrome, eGFRcr = CKD-EPI creatinine estimated GRF equation, eGFRcrcyst = CKD-EPI creatinine–cystatin C estimated GRF equation, eGFRcyst = CKD-EPI cystatin C estimated GRF equation, GFR = glomerular filtration rate, HF = heart failure, IDI = integrated discrimination improvement, MRA = mineralocorticoid receptor antagonist, NRI = Net Reclassification Index, Receptor Blocker, TTE = transthoracic echocardiography, WRF = worsening renal function.

Keywords: cardiorenal syndrome, chronic kidney disease, creatinine, cystatin C, eGFR, heart failure

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Acute heart failure (AHF) is a high mortality end-stage clinical syndromes of various cardiovascular disorders and is a major cause of death globally.[1] Due to the economic improvement and extending human life, morbidity and mortality of heart failure (HF) are growing worldwide. Also, composition of HF patients have increased number of elder patients and increased prevalence of related comorbidities.

In AHF, the dysfunction of heart and kidney resulting in a cascade of feedback mechanism causing damage to both organs and developing cardiorenal syndrome (CRS), which led to acute kidney injury (AKI) chronic kidney disease (CKD), and/or worsening renal function (WRF).[2,3] Despite recent advances in management and treatment, it remains one of the most important comorbidities in HF patients and is associated with adverse clinical outcomes.

Glomerular filtration rate (GFR) describes the flow rate of filtered fluid through the kidney which reflects and quantifies the renal function. The association between GFR and risk of mortality in patients with AHF has shown in various studies.[2,4] Accurate measurement of patient's renal function is critical to optimal management. The "gold standard" for GFR determination is to measure the clearance of exogenous substances, but these measurements are usually time-consuming and complicated for routine clinical practice.[5] Therefore, estimated glomerular filtration rate (eGFR) calculated by different formulas based on biochemicals that can mimic the clearance of glomerular filtration has been widely used in daily practice.

These methods such as MDRD,[6] Cockcroft-Gault formula,[7] Pottel-Lyon equation,[8] Pottel-Belgium equation,[8] Bedside Schwartz equation,[9] etc. have showed their promising effects on various clinical settings. Among, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations based on creatinine and/or cystatin C[10,11] are the most common used method in eGFR calculation.

However, the evaluation effects in patients with AHF affect by the serum concentration of the biomarkers and various pathophysiological factors. For instance, eGFR based on creatinine showed relatively imprecise owing to variation such as age, sex, muscle mass, physical activity and diet.[12] On the other hand, circulating cystatin C considered as a more sensitive and stable biomarker than creatinine in early renal impairment.[13] Also, study showed GFR based on creatinine substantially overestimated GFR in patients with AHF.[14] Overall, these results are debatable and there are lack of data in comparing the prognostic impact of GFR based on cystatin C and creatinine.

Therefore, our study aimed to compared the prognostic value of 3 CKD-EPI equations based on different serum biochemicals - creatine and cystatin C in patients with AHF.

2. Methods

2.1. Study design and participants

Our study included 354 patients hospitalized for AHF in Cardiology Department of the First Affiliated Hospital of Nanjing Medical University (Nanjing, China) from January 2012 to June 2016 (Fig. 1). All participants were age over 18 years old. AHF refers to the rapid onset or deterioration of symptoms and signs of heart failure which included new-onset AHF and acute decompensated heart failure (ADHF). Patients were diagnosed according to Chinese guideline for diagnosis and treatment of acute heart failure.[15] Patients received the standard medications for treatment - included diuretics, angiotensin converting enzyme inhibitor/ angiotensin receptor blocker (ACEI/ARB), beta-blocker and mineralocorticoid receptor antagonist (MRA).

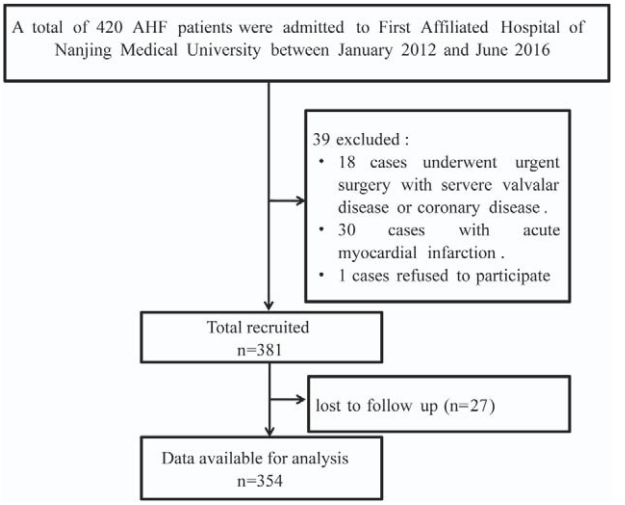

Figure 1. Flow chart of the study selection.

Major events and complications occurred during hospitalization were documented as comorbidities according to the guidelines[16–18] at the time of hospitalization. Excluded the patients diagnosed with malignant tumor, cognitive deficit, dementia, severe mental illness, and uncontrolled systemic disease (e.g., unstable or uncompensated respiratory, hepatic disease).

Our study was in accordance with the Declaration of Helsinki. All participants provided written informed consent, and the study was approved by the independent Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (Approval No. 2011-SR-012). The trial was registered at http://www.chictr.org.cn/ (ChiCTR - ONC - 12001944).

2.2. Data collection

Demographics, physical examination, laboratory results, clinical data, medical history and etiology of AHF were obtained within the first 24 hours after admission. All venous blood samples were obtained at the admission and analyzed in the central laboratory of our hospital. Creatinine and cystatin C were measured using the same blood sample tube by Beckman Coulter auto-analyzer AU 5800 (Beckman Coulter, USA). Transthoracic echocardiography (TTE) was obtained by Vivid E9 ultrasound system (GE Medical System, USA).

Estimated glomerular filtration rate were calculated based on different CKD-EPI equations[10,11] including CKD-EPI creatinine equation (eGFRcr), the CKD-EPI cystatin C equation (eGFR-cyst), and the CKD-EPI creatinine–cystatin C equation (eGFRcr-cyst). Detailed equation are shown in Supplemental Digital Content (Appendix 1, http://links.lww.com/MD/F125).

2.3. Endpoint and follow-up

The primary endpoint was all-cause mortality during the follow up. Endpoint and status of the patients were evaluated every 3

months in out-patient visit and/or telephone follow-up with confirmation of their family or physician.

2.4. Statistical analysis

Continuous variables are expressed as means with standard deviations (SDs) or median with interquartile range, and were compared using the unpaired Students *t* test or the Mann–Whitney *U* test, depending on whether they were normally distributed, as revealed by the Kolmogorov–Smirnov test. The median values and the frequencies of different CKD-EPI formula based on creatinine and/or cystatin C were compared using paired *t* test. Categorical variables are presented as numbers (%) and were compared using the Pearson χ^2 test. Associations of different equation with all-cause mortality during follow-up were assessed using Cox proportional hazard regression analyses with results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Variables with $P < .05$ in the univariate analysis were incorporated into the adjustment sets as follows:

1. unadjusted;
2. age and sex adjusted;
3. age, sex, NYHA class, NTproBNP, sodium, diabetes, systolic blood pressure, anemia adjusted.

Survival differences were compared using the Kaplan–Meier analysis and log-rank test. The predictive power of different CKD-EPI formulas were compared using receiver operator characteristic (ROC) curve analysis. Then, the predictive accuracy were evaluated by integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI) methods to compare the discriminative prognostic value. *P* values <.05 were considered as statistically significant. All statistical analyses were performed with the aid of R ver.3.6.0.

3. Results

3.1. Patient characteristics

During a median follow-up of 35 (18–46) months, 161 for patients have passed away. Patients were divided into 2 groups according to the primary endpoint. Baseline characteristics of studied population are presented in Table 1: Baseline Characteristics.

Age, sex, diastolic blood pressure, uric acid, hemoglobin, NT-proBNP, NYHA class, creatinine, and cystatin C were statistically significant between groups (All $P < .05$). In addition, there were no significant difference in other biochemical characteristics (potassium, sodium, calcium, albumin), ECG parameters, admission oral medication regimen, and etiologies between 2 groups.

3.2. Comparative analysis of different formula

The eGFR according to the 3 CKD-EPI equations were all significantly different between survival and death groups (eGFRcr: 79.1[63.2–94.2] vs 69.1[44.8–86.5], $P < .001$); eGFR-cyst: 56.6[43.4–71.2] vs 45.4[31.9–60.1], $P < .001$; eGFRcrcyst: 67.4[52.3–79.6] vs 55.9[36.3–67.9], $P < .001$).

The median values and interquartile range of eGFR by the 3 equations were 72.9 [55.4–91.3] for eGFRcr, 61.6 [46.1–74.7] for eGFRcrcyst and 52.0 [38.5–64.7] for eGFRcyst. There were significant differences between the 3 methods in eGFR evaluation (Fig. 2, $P < .001$).

Table 1

Baseline characteristics.

	Survival (n = 193)	All-cause death (n = 161)	*P* value
Age, year	58.7 (16.4)	64.5 (15.0)	.001
Male	141 (73.1%)	91 (56.5%)	.001
Hypertension	100 (51.8%)	79 (49.1%)	.607
Diabetes mellitus	52 (26.9%)	40 (24.8%)	.654
Cigarette	82 (42.5%)	54 (33.5%)	.085
BMI, kg/m^2	24.5 (4.21)	24.3 (4.59)	.693
Heart rate, bpm	86.0 (21.6)	84.4 (22.2)	.511
Systolic blood pressure, mm Hg	127 (22.7)	123 (19.6)	.094
Diastolic blood pressure, mm Hg	79.5 (15.7)	76.0 (12.0)	.020
Potassium, mmol/L	3.96 (0.46)	4.00 (0.52)	.411
Sodium, mmol/L	140 (10.4)	140 (4.15)	.798
Calcium, mmol/L	2.26 (0.15)	2.20 (0.55)	.143
Albumin, g/L	37.6 (4.85)	36.3 (5.02)	.143
Uric acid, μmol/L	474 (155)	510 (195)	.049
Hemoglobin, g/L	136 (19.4)	128 (20.6)	.000
NTproBNP, ng/L	1676[1087–4166]	2777[1563–6883]	<.001
NYHA class			.003
II	43 (22.3%)	16 (9.9%)	
III	105 (54.4%)	91 (56.5%)	
IV	45 (23.3%)	54 (33.5%)	
Etiology of AHF			.387
ICM	47 (24.4%)	43 (26.7%)	
VHD	30 (15.5%)	39 (24.2%)	
DCM	68 (35.2%)	48 (29.8%)	
HCM	23 (11.9%)	15 (9.3%)	
HHM	12 (6.2%)	8 (5.0%)	
Others	11 (5.7%)	8 (5.0%)	
Echocardiogram			
LVEF, %	40.7 (14.3)	43.5 (15.4)	.075
LVDd, mm	62.2 (11.8)	60.7 (13.0)	.240
LVDs, mm	40.7 (14.3)	47.8 (14.5)	.075
Admission oral medication			
ACEI/ARB	159 (82.4%)	125 (77.6%)	.264
β blocker	154 (79.8%)	132 (82.0%)	.602
loop diuretic	188 (97.4%)	153 (95.0%)	.236
MRA	178 (92.2%)	147 (91.3%)	.659
Nitrates	82 (42.5%)	70 (43.5%)	.851
Renal function			
Creatine, mg/dl	0.97[0.80–1.18]	1.07[0.86–1.07]	.012
Cystatin C, mg/L	1.24[1.09–1.50]	1.46[1.19–1.83]	<.001
eGFR			
eGFRcr, mL/min/1.73 m^2	79.1[63.2–94.2]	69.1[44.8–86.5]	<.001
eGFRcyst, mL/min/1.73 m^2	56.6[43.4–71.2]	45.4[31.9–60.1]	<.001
eGFRcrcyst, mL/min/1.73 m^2	67.4[52.3–79.6]	55.9[36.3–67.9]	<.001

Data are presented as mean (SD) or median [interquartile range], or n (%).ACEI/ARB = angiotensin converting enzyme inhibitors/ angiotensin receptor blocker, AHF = acute heart failure, DCM = dilated cardiomyopathy, eGFRcr = glomerular filtration rate estimated by plasma creatinine, eGFRCyst = glomerular filtration rate estimated by plasma cystatin C, eGFRcrcyst = glomerular filtration rate estimated by the combined creatinine/cystatin C equation, HCM = hypertrophic cardiomyopathy, HHD = hypertensive heart disease, ICM = ischemic cardiomyopathy, LVDd = left ventricular end-diastolic dimension, LVDs = left ventricular end-systolic dimension, LVEF = left ventricular ejection fraction, MRA = mineralocorticoid receptor antagonist, NTproBNP = N-terminal pro-brain natriuretic peptide, NYHA = New York Heart Association classification, VHD = valvular heart disease.

3.3. Predictive value of eGFR

To further explore the impact of different equation on AHF patients, especially patients with renal impairment (eGFR values below 60 ml/minute/1.73 m^2). All patients were regrouped according to the eGFR less or more than 60 ml/minute/1.73 m^2 by the 3 CKD-EPI equation.

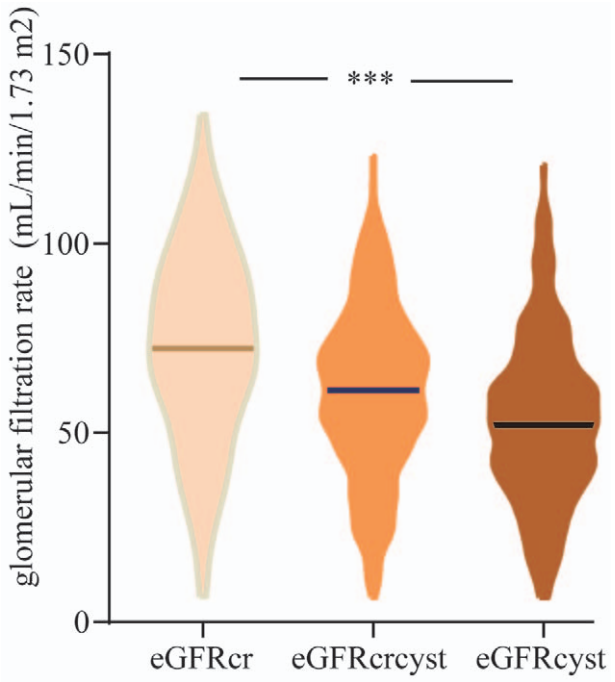

Figure 2. Comparison of estimated glomerular filtration rate (eGFR) calculated by different equations (*** represent $P < .001$).

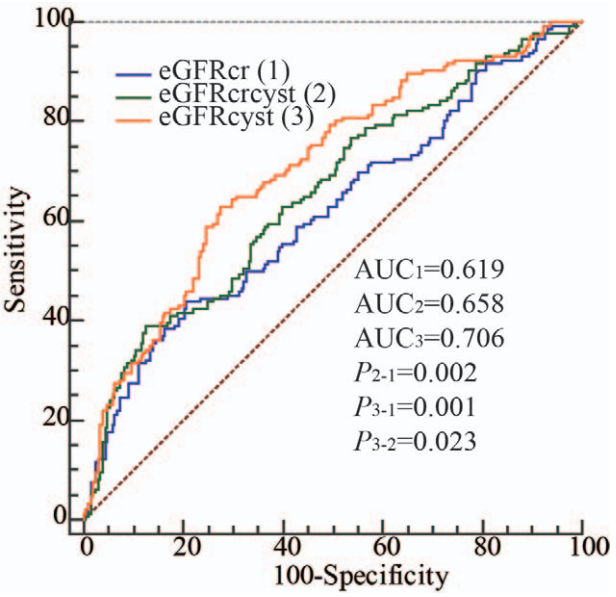

Figure 3. Receiver operator characteristic curve analysis for the prediction of all-cause mortality.

Kaplan–Meier analysis was used to estimate the time-to-event for death, the risk of all-cause mortality significantly increased in accordance with all 3 CKD-EPI formulas: eGFRcr (HR: 2.02, 95%CI [1.47–2.77], $P < .001$), eGFRcyst (HR: 1.92, 95%CI [1.35–2.74], $P < .001$), and eGFRcrcyst (HR: 1.86, 95%CI [1.36–2.55], $P < .001$).

After fully adjustment with demographic and clinical factors that associated with the prognosis of heart failure (age, sex, NYHA class, NTproBNP, sodium, diabetes, systolic blood pressure, hemoglobin), eGFRcr (HR: 0.93, 95%CI [0.85–1.01], $P = .076$) did not show significance. On the other hand, reduced eGFRcyst (HR: 0.84, 95%CI [0.76–0.93], $P = .001$) and eGFRcrcyst (HR: 0.87, 95%CI [0.79–0.96], $P = .004$) remained significant association (Table 2).

3.4. ROC analysis and comparison of different formulas

ROC analysis for the all-cause mortality between the formulas were performed. The area under curve (AUC) of eGFRcyst (0.706) was the greatest among the 3 formulas (Fig. 3). The difference between the AUCs of 3 CKD-EPI formulas were statistically significant (All $P < .05$), the AUC of eGFRcyst was significantly superior to both eGFRcr ($P = .001$) and eGFRcrcyst ($P = .023$) for the prediction of all-cause mortality.

3.5. Reclassification analysis

With the results above, continuous net reclassification index (cNRI) and integrated discrimination improvement (IDI) methods were calculated for a further comparison of the 3 equations (Table 3).

Both eGFRcyst (IDI = 7.3%, 95%CI [3.6–10.8], $P < .001$; cNRI = 19.6%, 95%CI [6–36.1], $P = .012$) and eGFRcrcyst (IDI = 4.3%, 95%CI [1.7–6.6], $P < .001$; cNRI = 8.7%, 95%CI [2.7–28.5], $P = .138$) showed certain improvement regarding the risk prediction compared with eGFRcr. In contrast, comparing eGFRcyst and eGFRcrcyst, eGFRcyst - equation using only cystatin C improved mortality stratification significantly (IDI = 3.0%, 95% CI [0–6.2], $P = .049$; cNRI = 11.1%, 95%CI [5.1–32.4], $P = .036$).

4. Discussion

Result demonstrated the eGFRcyst had the best prognostic value among 3 CKD-EPI equations in patient with AHF. Although all 3

Table 2

Predictive value of estimated glomerular filtration rate (eGFR) to all-cause mortality.

	eGFRcr (+10 ml/min/1.73 m^2)		eGFRcyst (+10 ml/min/1.73 m^2)		eGFRcrcyst (+10 ml/min/1.73 m^2)	
Outcome level of adjustment	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Model 1	0.86 (0.81,0.92)	<.001	0.78 (0.73,0.86)	<.001	0.82 (0.75,0.89)	<.001
Model 2	0.89 (0.82,0.95)	.001	0.81 (0.74,0.89)	<.001	0.84 (0.77,0.91)	<.001
Model 3	0.93 (0.85,1.01)	.076	0.84 (0.76,0.93)	.001	0.87 (0.79,0.96)	.004

model 1: unadjusted.

model 2: age and sex adjusted.

model 3: age, sex, NYHA class, NTproBNP, sodium, diabetes, systolic blood pressure, anemia fully adjusted.

CI = confidence interval, HR = hazard ratio, eGFRcr = glomerular filtration rate estimated by plasma creatinine, eGFRcyst = glomerular filtration rate estimated by plasma cystatin C, eGFRcrcyst, glomerular filtration rate estimated by the combined creatinine/cystatin C equation.

Table 3

Integrated discrimination improvement and net reclassification improvement for comparing estimated glomerular filtration rate (eGFR) by the 3 equations.

	Integrated discrimination improvement (IDI)			Net reclassification improvement (NRI)		
All-cause mortality	IDI (%)	CI (95%)	*P*	NRI (%)	CI (95%)	*P*
eGFRcyst vs eGFRcr	7.3	3.6–10.8	<.001	19.6	6–36.1	.012
eGFRcrcyst vs eGFRcr	4.3	1.7–6.6	<.001	8.7	2.7–28.5	.138
eGFRcyst vs eGFRcrcyst	3.0	0–6.2	.049	11.1	5.1–32.4	.036

CI = confidence interval, eGFRcr = glomerular filtration rate estimated by plasma creatinine, eGFRcyst = glomerular filtration rate estimated by plasma cystatin C, eGFRcrcyst = glomerular filtration rate estimated by the combined creatinine/cystatin C equation.

eGFR equations were shown significance in the baseline analysis, there were significant differences between the formulas. Also, both CKD-EPI formulas accounted with cystatin C (eGFRcyst and eGFRcrcyst) were associated to the all-cause mortality significantly after fully adjustment with other risk factors. Then, further analysis showed that eGRFcyst had the strongest association with mortality compared with the other 2 methods.

eGFR calculated by CKD-EPI equations with creatinine and cysctatin C are commonly used in assessment of renal function. However, the usages in different clinical settings are controversial. A comparative study by Rule et al concluded that eGFRcyst improved the estimation of GFR in patients with CKD, but the association between most of the risk factors was more accurate by eGFRcr.[19] On the contrary, there were studies suggested that the eGFRcrcyst had a better evaluation values and performed a better confirmatory test for CKD as a less biased method than the solo equations in elderly individuals.[12,20] Recently, UK Biobank study showed that eGFRcyst had the strongest association with cardiovascular diseases and mortality in general population.[21]

In both acute and chronic settings of heart failure, renal dysfunction and WRF are highly prevalent and associated with poor outcomes. The evaluating values are controversial as well.

When in steady state such as CHF, there is an inverse relationship between creatinine/cystatin C and GFR, allowing GFR to be estimated from either using simple equations.[22] Studies have showed CDK-EPI equations with cystatin C tended to have more accurate prognostic value regarding the assessment of renal function in patients with chronic heart failure (CHF). Study by Zamora et al showed both CKD-EPI equations containing cystatin C showed better prognostic performance in CHF patients than creatinine based eGFR.[23] Kervella et al reported eGFRcyst was more accurately diagnosed reduced kidney function than eGFRcr in patients with HF as well.[14]

But there were lack of studies regarding in acute setting HF, and the results were inconsistency. There was a study by Manzano-Fernández et al[24] demonstrated there was no significance between eGFRcyst and eGFRcrcyst CKD-EPI equation in ADHF patients and offered similar prognostic information, but it is worth noticing that the results were inconsistent with our study. Compared the 2 study design, their measurement of creatinine and other biochemicals were within 48 hours after admission, which might affect the evaluation and cause bias.

Creatinine is a product of muscle metabolism and a common marker of kidney function. Due to the different pathophysiological mechanisms of AHF, patient could rapidly develop AKI and renal dysfunction. Creatinine is a marker of kidney function, not injury. Therefore, the half-life of the serum creatinine is prolonged and required to reach a new steady-state level up to days depending the degree of renal insufficiency.[25,26] However, eGFRcr has been shown to overestimate the GFR in heart failure when it is compared with the other 2 equations.[27] Therefore, changes in serum creatinine are more suitable for defining and staging AKI in AHF patients. Applying admission creatinine to estimate GFR in AHF could misinterpret the renal function and prognostic value.

On the other hand, cystatin C is produced at a constant rate by nucleated cells and released into bloodstream with a much shorter half-life of 2 hours. Also, cystatin C is less affected by age, gender, weight, inflammation, and other factors compared with creatinine.[28,29] Previous study also demonstrated that eGFRcyst was more closely associated with mortality compared to both eGFRcr and eGFRcrcyst in unselected patients.[30] In various cardiometabolic conditions, cystatin C are associated with higher levels and has emerged as a of renal function biomarker that has been found to predict adverse outcomes of HF.[15,23,31] eGFRcyst was significantly lower than eGFRcr and eGFRcrcyst in these studies. In our study, results are consistent with previous study and consisted with the theory above which suggested eGRFcyst might provide a better prognostic value in the early onset of AHF. Our data also provided the additional evidence for evaluating admission renal function especially in AHF patients. These findings are useful especially for area with limited resources, the use of eGFRcyst enables clinicians to have a better first glance to the condition and prognosis of AHF patients in the early admission, and to guide the following optimal treatment decisions.

Our study has certain limitations. This study is a single-center cohort study and only documented all-cause mortality as endpoint. Second, eGFR function was measured only once and did not compared with direct measured GRF. There are a huge gap in eGFR and gold standard GRF in various conditions including HF. Larger scale study of these factors and relationship between renal function in patients with AHF is needed.

5. Conclusions

Our study found that the predictive value of eGFRcyst in the long-term mortality of patients with AHF was greater than both eGFRcr and eGFRcrcyst. Result could better guide the risk stratification in AHF patients for optimal management.

Author contributions

Iokfai Cheang and Shengen Liao contributed equally to this work.

IFC participated in design of the research and a major contributor in writing the manuscript. SGL drafted the manuscript and

performed the analysis of the study statistic design. XYL and RRG contributed data collection, investigation, visualization, and validation. WMY, YLZ and HFZ supervised the study program and method feasibility. XLL contributed conception and design of the research, and also performed critical revision of the manuscript for important intellectual content.

All authors had read and commented on the manuscript, gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

References

[1] Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63: 1123–33.

[2] Lawson CA, Testani JM, Mamas M, et al. Chronic kidney disease, worsening renal function and outcomes in a heart failure community setting: A UK national study. Int J Cardiol 2018;267:120–7.

[3] Smith GL, Lichtman JH, Bracken MB, et al. Renal impairment and outcomes in heart failure: Systematic review and meta-analysis. J Am Coll Cardiol 2006;47:1987–96.

[4] Rangaswami J, Bhalla V, Blair JEA, et al. American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical CardiologyCardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation 2019;139:e840–78.

[5] Feng JF, Qiu L, Zhang L, et al. Multicenter study of creatinine- and/or cystatin C-based equations for estimation of glomerular filtration rates in Chinese patients with chronic kidney disease. PLoS One 2013;8:e57240.

[6] Levey AS, Coresh J, Greene T, et al. Chronic Kidney Disease Epidemiology CollaborationExpressing the modification of diet in renal disease study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007;53:766–72.

[7] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.

[8] De Souza V, Pottel H, Hoste L, et al. Can the height-independent Pottel eGFR equation be used as a screening tool for chronic kidney disease in children? Eur J Pediatr 2015;174:1225–35.

[9] Pottel H, Dubourg L, Goffin K, et al. Alternatives for the bedside schwartz equation to estimate glomerular filtration rate in children. Adv Chronic Kidney Dis 2018;25:57–66.

[10] Levey AS, Stevens LA, Schmid CH, et al. CKD EPIA new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.

[11] Inker LA, Eckfeldt J, Levey AS, et al. Expressing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) cystatin C equations for estimating GFR with standardized serum cystatin C values. Am J Kidney Dis 2011;58:682–4.

[12] Inker LA, Schmid CH, Tighiouart H, et al. CKD-EPI InvestigatorsEstimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–9.

[13] Shimizu-Tokiwa A, Kobata M, Io H, et al. Serum cystatin C is a more sensitive marker of glomerular function than serum creatinine. Nephron 2002;92:224–6.

[14] Kervella D, Lemoine S, Sens F, et al. Cystatin C versus creatinine for GFR estimation in CKD due to heart failure. Am J Kidney Dis 2017;69:321–3.

[15] Chinese Society of Cardiology of Chinese Medical Association, Editorial Board of Chinese Journal of CardiologyGuideline for diagnosis and treatment of heart failure 2014. Zhonghua Xin Xue Guan Bing Za Zhi 2014;42:98–122.

[16] National Kidney FoundationK/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39:S1–266.

[17] Liu LS. Writing Group of 2010 Chinese Guidelines for the Management of Hypertension2010 Chinese guidelines for the management of hypertension (in Chinese). Chin J Cardiol 2011;39:579–615.

[18] American Diabetes AssociationDiagnosis and classification of diabetes. Diabetes Care 2011;34:S62–69.

[19] Rule AD, Bailey KR, Lieske JC, et al. Estimating the glomerular filtration rate from serum creatinine is better than from cystatin C for evaluating risk factors associated with chronic kidney disease. Kidney Int 2013;83: 1169–76.

[20] Fan L, Levey AS, Gudnason V, et al. Comparing GFR estimating equations using cystatin C and creatinine in elderly individuals. J Am Soc Nephrol 2015;26:1982–9.

[21] Lees JS, Welsh CE, Celis-Morales CA, et al. Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. Nat Med 2019;25:1753–60.

[22] Ruocco G, Palazzuoli A, Ter Maaten JM. The role of the kidney in acute and chronic heart failure. Heart Fail Rev 2020;25:107–18.

[23] Zamora E, Lupón J, de Antonio M, et al. Long-term prognostic value for patients with chronic heart failure of estimated glomerular filtration rate calculated with the new CKD-EPI equations containing cystatin C. Clin Chem 2014;60:481–9.

[24] Manzano-Fernández S, Flores-Blanco PJ, Pérez-Calvo JI, et al. Comparison of risk prediction with the CKD-EPI and MDRD equations in acute decompensated heart failure. J Card Fail 2013;19:583–91.

[25] Chiou WL, Hsu FH. Pharmacokinetics of creatinine in man and its implications in the monitoring of renal function and in dosage regimen modifications in patients with renal insufficiency. J Clin Pharmacol 1975;15:427–34.

[26] Fan PC, Chang CH, Chen YC. Biomarkers for acute cardiorenal syndrome. Nephrology (Carlton) 2018;23(Suppl 4):68–71. doi:10.1111/nep.13473.

[27] Ishigo T, Katano S, Yano T, et al. Overestimation of glomerular filtration rate by creatinine-based equation in heart failure patients is predicted by a novel scoring system [published online ahead of print, 2020 Jun 18]. Geriatr Gerontol Int 2020;10.1111/ggi.13959. doi:10.1111/ggi.13959.

[28] Arimoto T, Takeishi Y, Niizeki T, et al. Cystatin C, a novel measure of renal function, is an independent predictor of cardiac events in patients with heart failure. J Card Fail 2005;11:595–601.

[29] Alge JL, Arthur JM. Biomarkers of AKI: a review of mechanistic relevance and potential therapeutic implications. Clin J Am Soc Nephrol 2015;10:147–55.

[30] Helmersson-Karlqvist J, Ärnlöv J, Larsson A. Cystatin C-based glomerular filtration rate associates more closely with mortality than creatinine-based or combined glomerular filtration rate equations in unselected patients. Eur J Prev Cardiol 2016;23:1649–57.

[31] Breidthardt T, Sabti Z, Ziller R, et al. Diagnostic and prognostic value of cystatin C in acute heart failure. Clin Biochem 2017;50:1007–13.