Prognostic Comparison of the Estimations of Renal Function in Patients With Acute Heart Failure

Yu-Lun Cheng, MD; Shih-Hsien Sung, MD, PhD; Hao-Min Cheng, MD, PhD; Jui-Tzu Huang, MD, PhD; Chao-Yu Guo, PhD; Pai-Feng Hsu, MD, PhD; Wen-Chung Yu, MD; Chen-Huan Chen, MD

Background: The prognostic significance of the eGFR calculated by either the four-level Race Chronic Kidney Disease-Epidemiology Collaboration study equation (CKD-EPI4R) or the Chinese-modified Modification of Diet in Renal Disease equation (cMDRD) has not been compared in Asian populations with acute heart failure (AHF).

Methods and Results: A total of 3,044 patients hospitalized for AHF were enrolled. The National Death Registry was linked to identify deaths within a 5-year follow-up. Net reclassification improvement (NRI) was calculated to compare the prognostic value of either eGFR equation. During a median follow-up of 23.3 months, 1,424 (47%) patients died. Both eGFR_{cMDRD} and eGFR_{CKD-EPI4R} were independently predictive of death in the total study population (hazard ratio and 95% confidence intervals per 1-SD: 0.76, 0.71–0.81 and 0.74, 0.70–0.79, respectively), and in the subgroups of either reduced (HFrEF) or preserved (HFpEF) ejection fraction, after accounting for important confounders. With reference to eGFR_{cMDRD}, eGFR_{CKD-EPI4R} may improve the NRI by 2.0% (0.8–3.2%) for the prediction of death. The prognostic value of the CKD stages categorized by eGFR_{CKD-EPI4R} significantly outperformed eGFR_{cMDRD} with a categorical NRI of 9.5% (4.7–14.3%) in the total study population, 11.5% in HFrEF, and 8.3% in HFpEF.

Conclusions: Both eGFR_{cMDRD} and eGFR_{CKD-EPI4R} were independently associated with long-term survival in patients with AHF. However, the CKD stages derived from eGFR_{CKD-EPI4R} improved the risk stratification of death, compared with eGFR_{cMDRD}.

Key Words: Chronic kidney disease; Glomerular filtration rate; Heart failure; Mortality

Impaired renal function has prevailed in patients hospitalized for heart failure (HF), and it is associated with poor clinical outcomes. The identification of renal dysfunction in patients with HF is thus crucial for risk stratification and subsequent tailored therapy. Accurate measurement of the glomerular filtration rate (GFR) by assessing the clearance of endogenous markers, such as inulin, is time-consuming and impracticable. Levey et al therefore developed an estimating equation for GFR that the Modification of Diet in Renal Disease (MDRD) study has adopted in clinical practice worldwide. Given racial discrepancies, Ma et al and Kong et al further proposed and validated a Chinese-modified MDRD (cMDRD) equation for better estimation of GFR in Chinese populations. Nowadays, the estimated GFR (eGFR) is the most used surrogate of renal function for the diagnosis of chronic kidney disease (CKD) and an indicator of the prognosis in various populations.

Given the cohort for development of the MDRD equation was existing CKD, the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation was established from a general population to demonstrate a better estimation of GFR. Next, racial coefficients were introduced to improve the performance of the original CKD-EPI equation for 4-level race (CKD-EPI4R, including Black, Asian, Native American and Hispanic, White and other).

Although the CKD-EPI equation may have outperformed the MDRD equation in HF patients in Western countries, the prognostic differences of these 2 equations have not been evaluated in Asian populations with HF. We therefore investigated the prognostic value of eGFR, derived from either the cMDRD or CKD-EPI4R equation, in an Asian cohort of acute HF (AHF). We further disclosed the dissimilarity of eGFR between the phenotypes of HF.
Patients who had been hospitalized during October 2003 to December 2012 for new or exacerbated symptoms and signs of HF,11,12 were enrolled into an intramural registry. Patients with severe liver cirrhosis (Child-Pugh score B or C), sepsis, or endstage renal disease requiring hemodialysis was excluded from this analysis. In brief, 3,182 patients were eligible for the registry, but 138 were excluded for lack of follow-up (12 patients), missing creatinine data (94 patients), or undergoing hemodialysis (32 patients). The associated medical records, including morbidities, prescriptions, and hematological and biochemistry data were retrieved from a web-based electronic recording system. The Review Committee of Taipei Veterans General Hospital approved the use of the registry data for research purposes.

The left ventricular ejection fraction (LVEF) was obtained from the 2D-guided M-mode echocardiography in accordance with the recommendations of the American Society of Echocardiography.13 HF with reduced EF (HFrEF) or with preserved EF (HFpEF) was defined as either LVEF<50% or ≥50%, respectively. The ratio of peak mitral inflow velocities at early (E) and late diastole (A), and right ventricular systolic pressure were also measured.

### Methods

**Table 1. Baseline Characteristics of the Study Population by Phenotype of Heart Failure**

| Variables            | Total (n=3,044) | HFrEF (n=1,208) | HFpEF (n=1,836) | P value |
|----------------------|----------------|-----------------|-----------------|---------|
| **Age, years**       | 75.6±13.1      | 72.5±14.7       | 77.8±11.5       | <0.001  |
| **Men, n (%)**       | 2,073 (68)     | 914 (76)        | 1,159 (63)      | <0.001  |
| **SBP, mmHg**        | 140±32         | 133±30          | 144±33          | <0.001  |
| **Heart rate, beats/min** | 88±23          | 92±24           | 86±22           | <0.001  |
| **Morbidities, n (%)** |               |                 |                 |         |
| Hypertension         | 1,860 (61)     | 652 (54)        | 1,208 (66)      | <0.001  |
| Diabetes             | 1,124 (37)     | 427 (35)        | 697 (38)        | 0.144   |
| CAD                  | 994 (33)       | 481 (40)        | 513 (28)        | <0.001  |
| AF                   | 884 (29)       | 350 (29)        | 534 (29)        | 0.838   |
| ACS                  | 384 (13)       | 189 (16)        | 195 (11)        | <0.001  |
| **Biochemistry**     |               |                 |                 |         |
| BUN, mg/dL           | 36±23          | 35±23           | 36±24           | 0.224   |
| Creatinine, mg/dL    | 1.9±1.6        | 1.8±1.4         | 2.0±1.6         | 0.004   |
| eGFRcMDRD, mL/min    | 62±35          | 65±34           | 60±35           | 0.001   |
| eGFRckd-Epi4R, mL/min| 48±26          | 52±27           | 46±26           | <0.001  |
| Sodium, mmol/L       | 139±5          | 139±4           | 139±5           | 0.442   |
| Potassium, mmol/L    | 4.0±0.7        | 4.0±0.7         | 4.0±0.7         | 0.445   |
| NT-proBNP, pg/mL (n=1,120)† | 8.6±1.4 | 9.0±1.2 | 8.4±1.5 | <0.001 |
| **Echocardiography** |               |                 |                 |         |
| LVEF, %              | 54±20          | 35±13           | 67±10           | <0.001  |
| E/A ratio            | 1.1±0.7        | 1.4±0.9         | 1.0±0.6         | <0.001  |
| RVSP, mmHg           | 44±17          | 45±17           | 43±17           | 0.001   |
| **Medications, n (%)** |               |                 |                 |         |
| β-blockers           | 1,347 (44)     | 607 (50)        | 740 (40)        | <0.001  |
| RAS inhibitors       | 1,970 (65)     | 791 (66)        | 1,179 (64)      | 0.390   |
| MRA                  | 1,201 (40)     | 603 (50)        | 598 (33)        | <0.001  |
| Loop diuretics       | 2,036 (67)     | 838 (69)        | 1,198 (65)      | 0.020   |

†Natural logarithm transformation. ACS, acute coronary syndrome; AF, atrial fibrillation; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD-Epi4R, Four-level Race Chronic Kidney Disease-Epidemiology Collaboration Group; cMDRD, Chinese-modified Modification of Diet in Renal Disease; E/A ratio, the ratio of peak mitral inflow velocities at early (E) and late diastole (A); eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; RAS inhibitors include angiotensin-converting enzyme inhibitor and angiotensin-receptor antagonist; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure.

For the calculation of the estimated glomerular filtration rate (eGFR), the cMDRD equation is:
\[
\text{eGFR}_{\text{cMDRD}} = 186 \times \left( \frac{\text{Scr}}{1.154^{\text{age}^{-0.203}} \times 0.742} \right) 
\times 1.233, \quad \text{where Scr is serum creatinine.}
\]

The CKD-Epi4R formula can be expressed as a single equation as following:

\[
\text{eGFR}_{\text{CKD-Epi4R}} = \frac{186 \times \left( \frac{\text{Scr}}{1.154^{\text{age}^{-0.203}} \times 0.742} \right) \times 1.233}{\text{SCR}}
\]
Follow-up
We linked the database to the National Death Registry for the clinical outcome of death. Patients were followed for up to 5 years. The National Death Registry database registers valid information according to the International Classification of Disease, 9th Revision (ICD-9). The ICD-9 codes for cardiovascular death were 390–459.15

Statistical Analysis
Data are presented as the mean±standard deviation (SD) for continuous variables, and as number and percentages for categorical variables. Student’s t-test or the \( \chi^2 \) test was used to conduct the comparisons. The NT-proBNP level was taken into natural logarithm transformation before the statistical analyses because of the skewed distribution.

\[
eGFR_{\text{CKD-EPI4R}} = 141 \times \min(\text{Scr} / \kappa, 1) \times \max(\text{Scr} / \kappa, 1)^{-1.209} \times 0.993^{\sigma} \times 1.018 \text{ if female} \times 1.052, \text{ if male, where } \kappa = 0.7 \text{ for females and 0.9 for males, } \sigma = -0.329 \text{ for females and } -0.411 \text{ for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1.}
\]

The stages of CKD were classified by eGFR according to the clinical guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative: \( \geq 60 \text{ mL/min/1.73 m}^2 \) (Stage 1 and Stage 2); 59–45 mL/min/1.73 m\(^2\) (Stage 3a); 44–30 mL/min/1.73 m\(^2\) (Stage 3b); 29–15 mL/min/1.73 m\(^2\) (Stage 4); and \(<15 \text{ mL/min/1.73 m}^2 \) (Stage 5). Patients with eGFR <60 mL/min/1.73 m\(^2\) were defined as having CKD.
Intraclass correlation coefficients and Cohen’s κ index were used to evaluate the agreements of eGFR or the stages of CKD, defined by eGFR\textsubscript{cMDRD} or eGFR\textsubscript{CKD-EPI4R}. The mean differences between the 2 eGFR equations were analyzed using the Bland-Altman method.\textsuperscript{16} Receiver-operating characteristic (ROC) curve analysis described the predictive values of eGFR\textsubscript{cMDRD} or eGFR\textsubscript{CKD-EPI4R} with 5-year mortality and the c-statistic test was used to compare the differences of areas under the curves.\textsuperscript{17} Cox proportional hazard models were used to evaluate eGFR in the prediction of 5-year death after accounting for confounders. The model performance with eGFR\textsubscript{CKD-EPI4R} compared with eGFR\textsubscript{cMDRD} was evaluated by using net reclassification improvement (NRI).\textsuperscript{18,19} We quantified the degree of correct classification according to the outcome by estimating the categorical NRI using cross-categories of eGFR for both formulas.\textsuperscript{20} Kaplan-Meier survival curve analysis was conducted to compare the prognoses of different CKD stages. The two-sided differences were considered statistically significant at the 0.05 significance level. Statistical analyses were performed using IBM SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA) and SAS software version 9.4 (SAS Inc., Carey, NC, USA).

Results
A total of 3,044 patients (75.6±13.1 years, 68% male, 40% HFrEF) constituted this study. The baseline characteristics are shown in Table 1. Compared with HFpEF, patients with HFrEF were younger and more likely to be men, and had lower admission systolic blood pressure, higher heart rate, less hypertension and more coronary artery disease. In addition, patients with HFrEF had better renal function, in terms of lower creatinine level, and higher eGFR\textsubscript{cMDRD} and eGFR\textsubscript{CKD-EPI4R}. The prevalence of diabetes or atrial fibrillation, and levels of blood urea nitrogen, sodium and potassium were comparable between the 2 groups. NT-proBNP was higher in patients with HFrEF than in those with HFpEF, and patients with HFrEF also had higher E/A ratio and right ventricular systolic pressure.

Agreement of eGFR Measurements
The Bland-Altman analysis showed the correlations and discrepancies between eGFR\textsubscript{cMDRD} and eGFR\textsubscript{CKD-EPI4R} (Figure 1). The value of eGFR\textsubscript{CKD-EPI4R} was generally lower than that of eGFR\textsubscript{cMDRD}, with a mean difference (95% confidence interval) of 13.5 (7.9, −34.9) mL/min/1.73 m\textsuperscript{2} (Figure 1B). The intraclass correlation coefficient of eGFR\textsubscript{cMDRD} and eGFR\textsubscript{CKD-EPI4R} was 0.968 (0.965, 0.970) (Figure 1A). When 51% of the study population (47% of HFrEF and 53% of HFpEF) was categorized as having CKD by eGFR\textsubscript{cMDRD}, 68% (64% of HFrEF and 70% of HFpEF) would have CKD as defined by eGFR\textsubscript{CKD-EPI4R} (Figure 2). The κ value of the 5 categories derived from the 2 formulas was 0.659 (0.634–0.684), which indicated a fair strength of agreement (Supplementary Table).

Prognostic Impact of eGFR
During a median follow-up of 23.3 months (interquartile range 8.1–45.3 months), 1,424 (47%) patients died. The Kaplan-Meier survival curve analyses demonstrated that severity of CKD, stratified by either eGFR\textsubscript{cMDRD} or eGFR\textsubscript{CKD-EPI4R}, was related to long-term mortality (Figure 3). The survival curves, stratified by the stages of CKD, were better separated by eGFR\textsubscript{CKD-EPI4R} than by eGFR\textsubscript{cMDRD} (X\textsuperscript{2}=137 and 125, respectively). Although 1,538 (50.5%) patients were classified as having CKD by eGFR\textsubscript{cMDRD}, 68% (64% of HFrEF and 70% of HFpEF) were classified as having CKD by eGFR\textsubscript{CKD-EPI4R} (Figure 1A). When 51% of the study population (47% of HFrEF and 53% of HFpEF) was categorized as having CKD by eGFR\textsubscript{cMDRD}, 68% (64% of HFrEF and 70% of HFpEF) would have CKD as defined by eGFR\textsubscript{CKD-EPI4R} (Figure 2). The κ value of the 5 categories derived from the 2 formulas was 0.659 (0.634–0.684), which indicated a fair strength of agreement (Supplementary Table).
Figure 4. Kaplan-Meier survival curve analysis related to the presence of CKD, defined by either or both the cMDRD and CKD-EPI equations. Abbreviations as in Figures 1,2.

Table 2. Cox Regression Analysis of 5-Year Total Mortality Rate *

| eGFR equation | HR per 1 SD† (95% CI) | X² | P value |
|---------------|------------------------|----|---------|
| Total population |                         |    |         |
| cMDRD         | 0.760 (0.713–0.811)    | 69 | <0.001  |
| CKD-EPI 4R    | 0.743 (0.698–0.791)    | 86 | <0.001  |
| HFrEF         |                         |    |         |
| cMDRD         | 0.690 (0.621–0.767)    | 48 | <0.001  |
| CKD-EPI 4R    | 0.694 (0.628–0.766)    | 52 | <0.001  |
| HFpEF         |                         |    |         |
| cMDRD         | 0.800 (0.737–0.869)    | 28 | <0.001  |
| CKD-EPI 4R    | 0.770 (0.710–0.836)    | 39 | <0.001  |

*Adjusted for age, sex, LVEF, sodium, hypertension, diabetes mellitus, and coronary artery disease. †The standard deviation (SD) of cMDRD and CKD-EPI was 34.6 and 26.3 mg/dL, respectively. HR, hazard ratio; CI, confidence interval. Other abbreviations as in Table 1.

Table 3. Performance of the Cox Proportional Hazard Models

|                  | cMDRD             | CKD-EPI 4R        | P value |
|------------------|-------------------|-------------------|---------|
| Total population |                   |                   |         |
| AUC (95% CI)     | 0.608 (0.588–0.628)| 0.615 (0.595–0.635)| 0.620   |
| NRI              | Ref.              | 2.0% (0.8–3.2%)   | 0.001   |
| Categorical NRI  | Ref.              | 9.5% (4.7–14.3%)  | <0.001  |
| HFrEF population |                   |                   |         |
| AUC (95% CI)     | 0.646 (0.615–0.677)| 0.656 (0.625–0.686)| 0.659   |
| NRI              | Ref.              | 1.0% (−0.0–1.9%)  | 0.054   |
| Categorical NRI  | Ref.              | 11.5% (4.0–19.0%) | 0.003   |
| HFpEF population |                   |                   |         |
| AUC (95% CI)     | 0.587 (0.561–0.614)| 0.593 (0.567–0.619)| 0.744   |
| NRI              | Ref.              | 1.9% (−0.1–4.0%)  | 0.066   |
| Categorical NRI  | Ref.              | 8.3% (2.0–14.6%)  | 0.010   |

AUC, area under the receiver-operating characteristic curve; NRI, net reclassification improvement. Other abbreviations as in Table 1.
Main Findings

The study revealed the major discrepancies of eGFR derived from either the CKD-EPI\textsubscript{AR} or cMDRD equation were in patients with preserved renal function. More patients would be categorized with CKD by eGFR\textsubscript{CKD-EPI4R} than by eGFR\textsubscript{cMDRD}. However, both eGFR\textsubscript{CKD-EPI4R} and eGFR\textsubscript{cMDRD} were independently correlated with the clinical outcomes of AHF. In addition, eGFR\textsubscript{CKD-EPI4R} may outperform eGFR\textsubscript{cMDRD} in predicting long-term survival in the homogenous Chinese population. The risk of death related to CKD stage was better predicted by using the CKD-EPI\textsubscript{AR} equation than by the cMDRD equation. The prognostic superiority of eGFR\textsubscript{CKD-EPI4R}, compared with eGFR\textsubscript{cMDRD}, remained consistent regardless of the phenotype of HF.

Development of the eGFR Equations

The measurement of renal function is recommended to recognize renal impairment and monitor kidney function for risk stratification and tailored therapy.\textsuperscript{14} GFR is an essential risk factor for clinical outcome in various populations.\textsuperscript{1,2} Although actual renal function can be obtained by calculating the renal clearance of $^{125}$I-iothalamate, $^{99m}$Tc-DTPA, or insulin,\textsuperscript{22} the generalizability is poor. Although serum creatinine level is widely used as a surrogate of renal function, its representativeness is of doubt
when age, sex and body weight also influence the creatinine level. Therefore, Levey et al first developed the MDRD equation to better quantify renal function.\textsuperscript{3} Given the MDRD equation may underestimate the GFR of individuals with normal renal function,\textsuperscript{23,24} the CKD-EPI equation was developed from a more heterogeneous population.\textsuperscript{7} The CKD-EPI equation was then validated to be more accurate than the MDRD equation, especially in patients with preserved renal function.\textsuperscript{7,25} The National Kidney Foundation has recommended reporting eGFR by using the CKD-EPI equation with every serum creatinine measurement.\textsuperscript{26}

In addition, race is also a major determinant of renal function because of different muscle mass and dietary habits.\textsuperscript{27} The MDRD or CKD-EPI equation did not perform well in the estimation of GFR in Asians,\textsuperscript{4,8} and the modified equations for either Chinese or Asians have improved the bias of estimation.\textsuperscript{5,6,8}

**Discrepancy Between Different eGFR Equations**

Given the present study did not measure the true values of GFR by assessing the clearance of exogenous markers, we were not able to evaluate the accuracy of either eGFR equation. However, Al-Wakeel et al reported that the CKD-EPI equation was more accurate than the MDRD equation for the estimation of GFR in a small population, compared with inulin clearance.\textsuperscript{28} In our study, eGFR\textsubscript{CKD-EPI4R} was lower than eGFR\textsubscript{MDRD} in all subjects by a mean difference of 13.5 mL/min, and the difference was more prominent when eGFR was greater. Therefore, the CKD-EPI\textsubscript{4R} equation would categorize a greater proportion of the study population as having CKD, compared with the cMDRD equation (68% vs. 51%). The result was in line with the findings of McAlistier et al in their meta-analysis of 20,754 patients with HF that the CKD-EPI equation demonstrated higher estimation of renal dysfunction than the MDRD equation.\textsuperscript{29} Our study may be the first to show that the CKD-EPI\textsubscript{4R} equation also recognized more cases of CKD than did the cMDRD equation in Asian patients with HF.

**Prognostic Value of eGFR**

Matsushita et al demonstrated that the CKD-EPI equation was more accurate for risk classification for death than the MDRD equation in patients with CKD or known risks of CKD.\textsuperscript{30} McAlistier et al in a pooled analysis of 20,754 patients with HF further showed the advantage of the CKD-EPI equation over the MDRD equation in the prediction of adverse clinical events.\textsuperscript{30} In the present study, both eGFR\textsubscript{CKD-EPI4R} and eGFR\textsubscript{MDRD} were predictive of long-term survival, independent of age, sex, LVEF, sodium level and comorbidities. Although the c-statistics for the prediction of 5-year death by eGFR\textsubscript{MDRD} (0.608) and eGFR\textsubscript{CKD-EPI4R} (0.615) were not significantly different, ROC curve analysis was not meant to evaluate prognostic discrepancies. On the other hand, NRI might be a better measure for comparing the predictive ability for survival. We also clarified that the CKD-EPI\textsubscript{4R} equation was a better prognostic tool than the cMDRD equation by showing better risk stratification and significant NRIs. The findings remained true in patients with either HF+EF or HFP+EF. In addition, subjects who were defined as having CKD by eGFR\textsubscript{CKD-EPI4R} but not eGFR\textsubscript{MDRD} actually carried a higher mortality risk, compared with those without CKD by both equations.

**Study Limitations**

Given that the present study was a single-center registry and an observational study, there were some biases arising from internal and external validities. Because the baseline characteristics were similar to other population-based HF cohorts,\textsuperscript{31} and we adjusted for all the observed confounders, the study results might be able to be extrapolated to other populations. Second, we did not apply the Taiwanese modified MDRD and CKD-EPI equations because of their popularity and the generalizability of these equations.\textsuperscript{32} Third, the medications prescribed before the index hospitalization were not recorded in the registry. We therefore were unable to analyze the influence of drugs on eGFR. Fourth, only NT-proBNP but not BNP data were available in the registry and NT-proBNP would be more likely affected by renal dysfunction. Given that the values of NT-proBNP were only available for one-third of the study population, we did not include NT-proBNP in the multivariate Cox regression analysis. Moreover, we did not measure the true GFR in this study for the comparisons. Further studies are warranted to fairly judge the accuracy of these 2 Asian-modified equations. Lastly, we did not comprehensively measure the indices of LV diastolic function; the E/A ratio is not an appropriate indicator of diastolic function.

**Conclusions**

Renal dysfunction is common in patients with HF and associated with worse outcome. In addition, there are critical criteria involving renal function for the prescription of HF medications, including renin-angiotensin system blockers and mineralocorticoid antagonists. Therefore, it is necessary to have an accurate estimation of renal function. The present study has shown that the CKD-EPI\textsubscript{4R} equation generally had lower estimates of GFR and defined more patients with CKD, compared with the cMDRD equation. The categorized CKD stages by CKD-EPI\textsubscript{4R} improved risk stratification in the prediction of death of patients with AHF, regardless of the HF phenotype. The study suggested mandatory calculation of eGFR by the CKD-EPI\textsubscript{4R} equation with measurement of serum creatinine for early identification of at-risk patients requiring tailored therapy.

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**Conflicts of Interest**

None declared.

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**Supplementary Files**

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-18-1013