

Prognostic abilities of different calculation formulas for the glomerular filtration rate in elderly Chinese patients with coronary artery disease

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Objective: As a standard indicator of renal function, the glomerular filtration rate (GFR) is vital for the prognostic analysis of elderly patients with coronary artery disease (CAD). Thus, the search for the calculation equation of GFR with the best prognostic ability is an important task. The most commonly used Modification of Diet in Renal Disease (MDRD) equation and the Chinese version (CMDRD) of the MDRD equation has many shortcomings. The newly developed Mayo Clinic quadratic (Mayo) and Chronic Kidney Disease (CKD) Epidemiology Collaboration (CKD-EPI) equations may overcome these shortcomings. Because the populations involved in these equation-related studies are almost completely devoid of subjects > 70 years of age, there are more debates on the performance of these equations in the elderly. This study was designed to compare the prognostic abilities of different calculation formulas for the GFR in elderly Chinese patients with CAD.

Methods: This study included 1050 patients (≥ 60 years of age) with CAD. The endpoint was all-cause mortality over a mean follow-up period of 417 days.

Results: The median age was 86 years (60–104 years). The median values for the MDRD-GFR, CMDRD-GFR, CKD-EPI-GFR, and Mayo-GFR were 66.0, 69.2, 65.6, and 75.8 mL/minute/1.73 m², respectively. The prevalence of GFR < 60 mL/minute/1.73 m² based on these measures was 39.3%, 35.4%, 43.0%, and 28.7%, respectively. Their area under the curve values for predicting death were 0.611, 0.610, 0.625, and 0.632, respectively. Their cut-off points for predicting death were 54.1, 53.5, 48.0, and 57.4 mL/minute/1.73 m², respectively. Compared with the MDRD-GFR, the net reclassification improvement values of the CMDRD-GFR, CKD-EPI-GFR, and Mayo-GFR were 0.02, 0.10, and 0.14, respectively.

Conclusion: The prognostic abilities of the CKD-EPI and Mayo equations were significantly superior to the MDRD and CMDRD equations; the Mayo equation had a mild, but not statistically significant superiority compared with the CKD-EPI equation in elderly Chinese patients with CAD.

Keywords: chronic kidney disease, coronary artery disease, glomerular filtration rate, equation, elderly

Introduction

On a global scale, evolving changes in demographics have led to an aging population, along with an increasing prevalence of renal function impairment in patients with coronary artery disease (CAD).¹ The latter might result in a higher mortality rate.^{2–4} Thus, as the standard indicator of renal function, the glomerular filtration rate (GFR) is vital for the prognostic analysis of elderly patients with CAD. To search for the calculation equation of GFR derived from serum creatinine (Scr) with the best prognostic ability is therefore an important task. The poorer prognostic ability of the most commonly used Modification of

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Diet in Renal Disease (MDRD) study equation in subjects with an elevated GFR, such as women, younger, and white subjects without comorbidities, has been well-established.⁵⁻⁷ The newly developed Mayo Clinic quadratic (Mayo) and Chronic Kidney Disease (CKD) Epidemiology Collaboration (CKD-EPI) equations consist of the same four variables as the MDRD equation, but may have better prognostic ability.⁸⁻¹⁰ Race is an important determinant of the GFR calculation. Unfortunately, Asians have not been included in MDRD and CKD-EPI studies; thus the Chinese MDRD (CMDRD) equation is based on the original MDRD equation for use in Chinese patients,¹¹ but there is still no modification of the CKD-EPI equation in the People's Republic of China. The populations involved in these equation-related studies were almost completely devoid of subjects > 70 years of age, subjects who are known to have the greatest burden of GFR-related adverse outcomes.^{8,9} Therefore, debates on the performance of these equations in the elderly continue.

Currently, there is no study that has compared the four equations in populations composed mainly of the elderly, men, and Chinese with CAD, as opposed to women, younger, and white subjects without comorbidities. Since these formulas may not perform equally in different subjects, the comparison made between the formulas depends on the subjects under study.¹² The current study was designed to compare the prognostic abilities of different calculation formulas for the GFR in elderly Chinese patients with CAD.

Methods

Population

Patients ≥ 60 years of age who were diagnosed with CAD were enrolled in this study. The diagnosis was based on history, symptoms of typical angina, cardiac markers, and specific cardiac examinations, such as an electrocardiogram (resting/exercise), echocardiography, radionuclide imaging, computed tomography, and coronary arteriography, and was performed by chief physicians or associate chief physicians according to the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines.^{13,14} The exclusion criteria included severe aortic stenosis, anticipated cardiac transplantation, and use of a left ventricular assist device. The current study was comprised of 1050 cases, on which the following analysis was based. The Chinese People's Liberation Army General Hospital was the designated hospital for all patients, and had integrated long-term medical and final death records, which made it easier for us to follow up effectively and judge endpoints accurately. The study protocol was approved by the local Ethics Committee

and in accordance with the Helsinki Declaration of 1975 (as revised in 1983).

Baseline variables

All information was carefully obtained, preserved, and verified by trained researchers. The basic characteristics included demographics (age and gender) and physical examination findings (mean systolic blood pressure). The body mass index was defined as the weight in kilograms divided by the square of the height in meters. The Scr concentration was measured using an enzymatic method, and the calibration formula was as follows:¹⁵

Jaffe's kinetic method:

$$\text{Scr (mg/dL)} = 0.795 \times [\text{enzymatic method Scr (mg/dL)}] + 0.29. \quad (1)$$

The enzymatic method Scr was used in the CKD-EPI formula, and the Jaffe's kinetic method Scr was used in the other three formulas. The GFR of all 1050 subjects was evaluated with different equations as follows.

MDRD formula:⁵

$$\text{MDRD} = 186 \times \text{Scr (mg/dL)}^{-1.154} \times \text{age (years)}^{-0.203} \times 0.742 \text{ (if female); } (2)$$

Chinese MDRD formula:¹¹

$$\text{CMDRD} = 175 \times \text{Scr (mg/dL)}^{-1.234} \times \text{age (year)}^{-0.179} \times 0.79 \text{ (if female); } (3)$$

Mayo Clinic quadratic formula:¹⁰

$$\text{Mayo} = \exp [1.911 + 5.249/\text{Scr (mg/dL)} - 2.114/\text{Scr (mg/dL)}^2 - 0.00686 \times \text{age (years)} - 0.205 \text{ (if female)}]; \quad (4)$$

CKD-EPI formula⁸

If female and if Scr ≤ 0.7 mg/dL:

$$\text{CKD - EPI} = 144 \times \text{Scr (mg/dL)}/0.7^{-0.329} \times 0.993^{\text{age (years)}} \quad (5)$$

If female and if Scr > 0.7 mg/dL:

$$\text{CKD - EPI} = 144 \times \text{Scr (mg/dL)}/0.7^{-1.209} \times 0.993^{\text{age (years)}} \quad (6)$$

If male and if Scr ≤ 0.9 mg/dL:

$$\text{CKD - EPI} = 141 \times \text{Scr (mg/dL)} / 0.9^{-0.411} \times 0.993^{\text{age (years)}} \quad (7)$$

If male and if Scr > 0.9 mg/dL:

$$\text{CKD - EPI} = 141 \times \text{Scr (mg/dL)} / 0.9^{-1.209} \times 0.993^{\text{age (years)}} \quad (8)$$

Determination of diseases

Hypertension was considered to be present if the systolic blood pressure was ≥ 140 mmHg, the diastolic blood pressure was ≥ 90 mmHg, and/or the subject was taking an antihypertensive drug. A subject was considered to have diabetes mellitus if the fasting plasma glucose was ≥ 7.0 mmol/L, the postprandial blood glucose (2-hour venous blood glucose) was ≥ 11.1 mmol/L, and/or the subject was taking a hypoglycemic drug or insulin. Atrial fibrillation (AF) and chronic heart failure (CHF) were defined on the basis of the ACC/AHA/ESC 2006 guideline for AF,¹⁶ and the ESC 2008 guideline for CHF,¹⁷ respectively.

Outcome

Given the priority of all-cause mortality in outcome studies, as well as the high incidence of multiple organ failure in the elderly, all-cause mortality was chosen as the endpoint and was ascertained from death records.

Statistical analysis

The variables were described by the mean and standard deviation for continuous variables with a normal distribution, the median and 25th–75th percentiles for nonnormally distributed continuous variables, and the percentage of the total for categorical variables. The differences between any two equations were tested by the Wilcoxon signed-rank test. The GFR was divided into six different categories (>90, 60–89, 45–59, 30–44, 15–29, and <15 mL/minute/1.73 m²). The differences between the GFR categories were tested by one-way analysis of variance for continuous variables (normal distribution), the Kruskal–Wallis test for continuous variables (abnormal distribution), and χ^2 analysis for categorical variables. The correlations between any two equations were determined with Spearman's test. The proportion of patients with a GFR < 60 mL/minute/1.73 m² was defined as the prevalence and the differences were examined with a Kappa test.

Not only the receiver-operating characteristic (ROC) curve and area under the curve (AUC) values, but also the net reclassification improvement (NRI), as described by Pencina

et al¹⁸ were used to assess the prognostic value of different equations. The best cut-off value of the GFR for predicting mortality was derived from the ROC curve, and was the cut-off point at which the sum of the sensitivity and specificity was the highest. The NRI was calculated as the sum of the proportion of participants reclassified downward to a lower GFR category for people who died and the proportion of participants reclassified upward to a higher GFR category for people who survived, minus the sum of the proportion of participants reclassified upward for people who died and the proportion of participants reclassified downward for people who survived. The Z statistic was used to compare the c-statistics and to determine the significance of NRI. To judge the independent predictive value of renal function impairment for mortality, covariates with a $P < 0.10$ were identified by Cox regression univariate analysis and taken into the multivariate Cox regression model with mortality as the dependent variable, which was divided into two steps, including the backward stepwise (likelihood ratio test) with a $P < 0.10$ and enter with a two-tailed $P < 0.05$ to avoid collinearity of the variables. The β value is the coefficient of variables in the Cox regression model, and the hazard ratio (HR) is the $\exp(\beta)$. Statistical analysis was conducted using the Statistical Package for the Social Sciences 17 (SPSS, Inc, Chicago, IL, USA) and MedCalc 11.6 for Windows (MedCalc Software bvba, Mariakerke, Belgium).

Results

The median age of the participants was 86 years (60–104 years), and 80.8% (848 patients) of the participants were >80 years of age. The majority (89.2%) of the participants were male, and all the participants were Chinese (100%). Table 1 lists the clinical characteristics of the participants at different GFR categories computed using four equations. The median values (25th–75th percentiles) for the MDRD-GFR, CMDRD-GFR, CKD-EPI-GFR, and Mayo-GFR were 66.0 (51.6, 78.0), 69.2 (53.3, 82.3), 65.6 (46.9, 80.2), and 75.8 (56.5, 88.5) mL/minute/1.73 m², respectively. The GFR computed by any two equations showed strong correlations (correlation coefficients: MDRD-GFR and CMDRD-GFR: 0.996; MDRD-GFR and CKD-EPI-GFR: 0.980; MDRD-GFR and Mayo-GFR: 0.959; CMDRD-GFR and CKD-EPI-GFR: 0.987; CMDRD-GFR and Mayo-GFR: 0.955; and CKD-EPI-GFR and Mayo-GFR: 0.963; all $P < 0.001$). The significant differences in the computed GFR were observed with respect to any two equations (all $P < 0.001$). As shown in Figure 1A, the GFR determined by each equation decreased as the 10-year age categories increased.

Table 1 Clinical characteristics of participants at different GFR categories computed using four equations

Characteristics	GFR categories (mL/minute/1.73 m ²)						P-value
	>90	60–89	45–59	30–44	15–29	<15	
Age (years)							
MDRD	86.0 (81.8–88.3)	85.0 (80.0–89.0)	86.0 (82.0–90.0)	88.0 (83.0–92.0)	87.0 (83.0–90.0)	83.5 (77.0–87.0)	<0.001
CMDRD	85.0 (80.0–89.0)	85.0 (80.3–89.0)	86.0 (83.0–90.0)	88.0 (82.5–92.0)	87.0 (83.0–90.0)	84.0 (77.0–87.0)	<0.001
CKD-EPI	78.0 (68.0–86.0)	85.0 (81.0–89.0)	86.0 (83.0–89.0)	88.0 (84.0–92.0)	88.0 (84.0–91.0)	84.5 (77.0–89.0)	<0.001
Mayo	83.0 (75.0–87.0)	86.0 (82.0–90.0)	87.0 (84.0–91.0)	88.0 (83.0–91.0)	88.0 (84.0–91.0)	83.5 (77.0–87.5)	<0.001
Men (%)							
MDRD	104 (98.1)	480 (90.4)	210 (87.9)	83 (79.0)	33 (84.6)	27 (90.0)	<0.001
CMDRD	150 (94.9)	467 (89.8)	178 (88.6)	81 (80.2)	33 (84.6)	28 (90.3)	0.010
CKD-EPI	71 (94.7)	470 (89.9)	195 (89.4)	110 (85.9)	54 (81.8)	37 (92.5)	0.145
Mayo	229 (100.0)	444 (85.4)	124 (90.5)	68 (81.9)	41 (87.2)	31 (91.2)	<0.001
BMI (kg/m²)							
MDRD	23.1 (3.5)	23.9 (3.4)	24.6 (3.6)	23.5 (3.4)	23.5 (3.4)	23.7 (3.7)	0.009
CMDRD	23.3 (3.5)	24.0 (3.4)	24.5 (3.5)	23.5 (3.4)	23.2 (3.5)	23.7 (3.7)	0.017
CKD-EPI	23.7 (3.8)	23.8 (3.3)	24.3 (3.6)	24.2 (3.5)	23.6 (3.4)	23.1 (3.6)	0.185
Mayo	23.6 (3.1)	24.0 (3.6)	24.5 (3.6)	23.6 (3.2)	23.5 (3.6)	23.3 (3.8)	0.119
MSBP (mmHg)							
MDRD	132.8 (13.5)	132.7 (13.6)	133.8 (12.6)	134.4(13.0)	134.9 (13.1)	137.9 (14.9)	0.258
CMDRD	132.2 (13.1)	133.0 (13.6)	133.7 (12.7)	134.1 (13.1)	135.0 (13.1)	137.8 (14.7)	0.332
CKD-EPI	131.7 (13.5)	132.6 (13.5)	134.4 (13.1)	133.6 (13.1)	134.0 (12.1)	139.1 (14.2)	0.040
Mayo	130.8 (12.3)	133.8 (13.8)	133.6 (12.7)	134.0 (13.4)	134.3 (11.9)	139.1 (14.8)	0.005
AMI (%)							
MDRD	5 (4.7)	30 (5.6)	16 (6.7)	13 (12.4)	3 (7.7)	4 (13.3)	0.105
CMDRD	8 (5.1)	27 (5.2)	16 (8.0)	13 (12.9)	2 (5.1)	5 (16.1)	0.018
CKD-EPI	5 (6.7)	26 (5.0)	15 (6.9)	14 (10.9)	5 (7.6)	6 (15.0)	0.060
Mayo	15 (6.6)	25 (4.8)	13 (9.5)	10 (12.0)	3 (6.4)	5 (14.7)	0.037
CHF (%)							
MDRD	15 (14.2)	130 (24.5)	90 (37.7)	59 (56.2)	21 (53.8)	12 (40.0)	<0.001
CMDRD	30 (19.0)	129 (24.8)	77 (38.3)	57 (56.4)	22 (56.4)	12 (38.7)	<0.001
CKD-EPI	14 (18.7)	125 (23.9)	77 (35.3)	63 (49.2)	31 (47.0)	17 (42.5)	<0.001
Mayo	36 (15.7)	155 (29.8)	51 (37.2)	47 (56.6)	25 (53.2)	13 (38.2)	<0.001
Hypertension							
MDRD	76 (71.7)	407 (76.6)	203 (84.9)	90 (85.7)	35 (89.7)	28 (93.3)	0.001
CMDRD	118 (74.7)	398 (76.5)	173 (86.1)	86 (85.1)	35 (89.7)	29 (93.5)	0.002
CKD-EPI	55 (73.3)	396 (75.7)	186 (85.3)	106 (82.8)	59 (89.4)	37 (92.5)	0.001
Mayo	169 (73.8)	411 (79.0)	116 (84.7)	71 (85.5)	40 (85.1)	32 (94.1)	0.014
DM (%)							
MDRD	42 (39.6)	201 (37.9)	98 (41.0)	44 (41.9)	23 (59.0)	9 (30.0)	0.137
CMDRD	66 (41.8)	191 (36.7)	84 (41.8)	44 (43.6)	22 (56.4)	10 (32.3)	0.133
CKD-EPI	32 (42.7)	194 (37.1)	85 (39.0)	60 (46.9)	32 (48.5)	14 (35.0)	0.217
Mayo	82 (35.8)	199 (38.3)	63 (46.0)	37 (44.6)	25 (53.2)	11 (32.4)	0.097
AF (%)							
MDRD	13 (12.3)	110 (20.7)	60 (25.1)	17 (16.2)	13 (33.3)	6 (20.0)	0.029
CMDRD	21 (13.3)	110 (21.2)	54 (26.9)	15 (14.9)	13 (33.3)	6 (19.4)	0.007
CKD-EPI	5 (6.7)	107 (20.5)	58 (26.6)	22 (17.2)	18 (27.3)	9 (22.5)	0.006
Mayo	37 (16.2)	114 (21.9)	34 (24.8)	12 (14.5)	16 (34.0)	6 (17.6)	0.036

Abbreviations: GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; CMDRD, Chinese MDRD equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; Mayo, Mayo Clinic quadratic equation; BMI, body mass index; MSBP, mean systolic blood pressure; AMI, acute myocardial infarction; CHF, chronic heart failure; DM, diabetes mellitus; AF, atrial fibrillation.

According to the MDRD-GFR, CMDRD-GFR, CKD-EPI-GFR, and Mayo-GFR, the prevalence of GFR < 60 mL/minute/1.73 m² in elderly patients with CAD was 39.3% (413 patients), 35.4% (372 patients), 43.0% (452 patients), and 28.7% (301 patients), respectively. Compared with

the MDRD-GFR, the prevalence of GFR < 60 mL/minute/1.73 m², according to the CMDRD-GFR (kappa value: 0.917, $P < 0.001$), CKD-EPI-GFR (kappa value: 0.908, $P < 0.001$), and Mayo-GFR (kappa value: 0.761, $P < 0.001$) showed significant differences. The number of patients in the

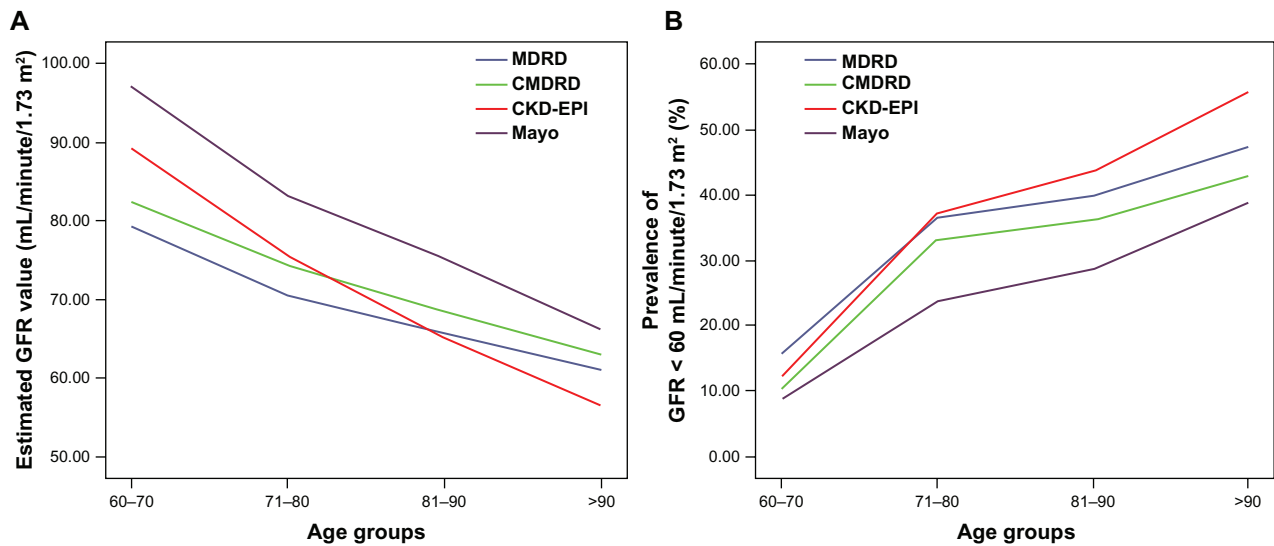


Figure 1 GFR determined by each equation and prevalence of a GFR < 60 mL/minute/1.73 m². **(A)** The GFR determined by each equation decreased as the 10-year age categories increased. **(B)** The prevalence of a GFR < 60 mL/minute/1.73 m² was proportional to the 10-year age categories. **Abbreviations:** GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; CMDRD, Chinese MDRD equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; Mayo, Mayo Clinic quadratic equation.

different GFR categories is reported in Table 2. The prevalence of GFR < 60 mL/minute/1.73 m² was proportional to the 10-year age categories (Figure 1B).

There was a mean follow-up period of 417 days (median: 319 days; 25th–75th percentiles: 185–557 days) for the entire cohort, with 218 deaths (20.8%). The mortality rates for each GFR category are displayed in Table 2. The mortality rates of the patients with a GFR < 60 mL/minute/1.73 m² determined by the MDRD, CMDRD, CKD-EPI, and Mayo equations were 8.6% (118 patients), 30.1% (112 patients), 28.5% (129 patients), and 33.6% (101 patients), respectively. Compared with the MDRD equation, the mortality rates of the patients with a GFR < 60 mL/minute/1.73 m² determined by other equations had no clear difference (CMDRD equation: *P* = 0.637; CKD-EPI

equation: *P* = 0.992; Mayo equation: *P* = 0.154). The AUC values for predicting death with respect to the MDRD-GFR, CMDRD-GFR, CKD-EPI-GFR, and Mayo-GFR were 0.611 [95% confidence interval (CI): 0.563–0.659], 0.610 (95% CI: 0.562–0.658), 0.625 (95% CI: 0.579–0.672), and 0.632 (95% CI: 0.586–0.677), respectively. Despite no significant difference between the MDRD-GFR and CMDRD-GFR (*P* = 0.651), the AUC values of the CKD-EPI-GFR and Mayo-GFR varied significantly from the MDRD-GFR and CMDRD-GFR (all *P* < 0.001). Compared with the CKD-EPI-GFR, a larger but statistically insignificant AUC value was observed with the Mayo-GFR (*P* = 0.244). The cut-off points for the MDRD-GFR, CMDRD-GFR, CKD-EPI-GFR, and Mayo-GFR with the best accuracy for predicting death were at 54.1 mL/minute/1.73 m² (sensitivity: 0.762; speci-

Table 2 Numbers of patients and mortality rates at each GFR category

Characteristics	GFR categories (mL/minute/1.73 m ²)					
	>90	60–89	45–59	30–44	15–29	<15
Numbers of patients (%)						
MDRD	106 (10.1)	531 (50.6)	239 (22.8)	105 (10.0)	39 (3.7)	30 (2.9)
CMDRD	158 (15.0)	520 (49.5)	201 (19.1)	101 (9.6)	39 (3.7)	31 (3.0)
CKD-EPI	75 (7.1)	523 (49.8)	218 (20.8)	128 (12.2)	66 (6.3)	40 (3.8)
Mayo	229 (21.8)	520 (49.5)	137 (13.0)	83 (7.9)	47 (4.5)	34 (3.2)
Mortality rates (%)						
MDRD	28 (26.4)	72 (13.6)	42 (17.6)	38 (36.2)	20 (51.3)	18 (60.0)
CMDRD	37 (23.4)	69 (13.3)	39 (19.4)	35 (34.7)	19 (48.7)	19 (61.3)
CKD-EPI	15 (20.0)	74 (14.1)	42 (19.3)	36 (28.1)	27 (40.9)	24 (60.0)
Mayo	40 (17.5)	77 (14.8)	30 (21.9)	26 (31.3)	24 (51.1)	21 (61.8)

Abbreviations: GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; CMDRD, Chinese MDRD equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; Mayo, Mayo Clinic quadratic equation.

ficity: 0.477), 53.5 mL/minute/1.73 m² (sensitivity: 0.797; specificity: 0.450), 48.0 mL/minute/1.73 m² (sensitivity: 0.787; specificity: 0.463), and 57.4 mL/minute/1.73 m² (sensitivity: 0.791; specificity: 0.454), respectively.

Compared with the MDRD-GFR, the CMDRD-GFR reclassified two (0.2%) to higher, and 96 (9.1%) to lower categories, the CKD-EPI-GFR reclassified 202 (19.2%) to higher, and 25 (2.4%) to lower categories, and the Mayo-GFR reclassified 38 (3.6%) to higher, and 268 (25.5%) to lower categories. Compared with the CKD-EPI-GFR, the Mayo-GFR reclassified 22 (2.1%) to higher and 429 (40.9%) to lower categories. The reclassification of patients in different GFR categories is shown in Table 3. The NRI in the risk of mortality was calculated and shown in Table 4. Compared with the MDRD-GFR and CMDRD-GFR, the NRI of the CKD-EPI-GFR was calculated at 0.10 and 0.09, and was highly significant ($P = 0.004$ and $P < 0.001$). Similar results were observed for the Mayo-GFR (NRI: 0.14, $P < 0.001$; NRI: 0.12, $P < 0.001$); however, there was no significant distinction in the NRI between the MDRD-GFR and CMDRD-GFR (NRI: 0.02, $P = 0.258$) or between the CKD-EPI-GFR and Mayo-GFR (NRI: 0.04, $P = 0.221$).

Based on univariate analysis, a GFR < 60 mL/minute/1.73 m² was associated with mortality regardless of the equation used (MDRD-GFR, HR: 1.98, 95% CI: 1.52–2.59, $P < 0.001$; CMDRD-GFR, HR: 2.14, 95% CI:

1.64–2.79, $P < 0.001$; CKD-EPI-GFR, HR: 2.10, 95% CI: 1.60–2.75, $P < 0.001$; Mayo-GFR, HR: 2.46, 95% CI: 1.88–3.20, $P < 0.001$). The associations of the MDRD-GFR < 54.1 mL/minute/1.73 m² (HR: 2.58, 95% CI: 1.98–3.37, $P < 0.001$), CMDRD-GFR < 53.5 mL/minute/1.73 m² (HR: 2.76, 95% CI: 2.11–3.60, $P < 0.001$), CKD-EPI-GFR < 48.0 mL/minute/1.73 m² (HR: 2.75, 95% CI: 2.11–3.60, $P < 0.001$), and Mayo-GFR < 57.4 mL/minute/1.73 m² (HR: 2.73, 95% CI: 2.09–3.56, $P < 0.001$) with higher mortality were all stronger. After adjusting for age, gender, CHF, acute myocardial infarction, AF, hypertension, diabetes mellitus, body mass index, and mean systolic blood pressure, patients with a GFR < 60 mL/minute/1.73 m² experienced a significantly higher mortality than patients with a GFR ≥ 60 mL/minute/1.73 m² (MDRD-GFR, HR: 1.57, 95% CI: 1.19–2.07, $P = 0.002$; CMDRD-GFR, HR: 1.63, 95% CI: 1.23–2.15, $P = 0.001$; CKD-EPI-GFR, HR: 1.62, 95% CI: 1.22–2.15, $P = 0.001$; Mayo-GFR, HR: 1.86, 95% CI: 1.40–2.46, $P < 0.001$). In addition, the MDRD-GFR < 54.1 mL/minute/1.73 m² (HR: 1.97, 95% CI: 1.48–2.60, $P < 0.001$), CMDRD-GFR < 53.5 mL/minute/1.73 m² (HR: 2.07, 95% CI: 1.54–2.75, $P < 0.001$), CKD-EPI-GFR < 48.0 mL/minute/1.73 m² (HR: 2.05, 95% CI: 1.54–2.72, $P < 0.001$), and Mayo-GFR < 57.4 mL/minute/1.73 m² (HR: 2.05, 95% CI: 1.54–2.72, $P < 0.001$) showed more identifiable relationships with mortality.

Table 3 The reclassification of patients at different GFR categories

GFR (mL/minute/1.73 m ²)	Reclassification	CMDRD ^a (MDRD)	CKD-EPI (MDRD)	Mayo (MDRD)	CKD-EPI (CMDRD)	Mayo (CMDRD)	Mayo (CKD-EPI)
>90	Upward ^b	0	0	0	0	0	0
	Unchanged	106	54	84	67	128	53
	Downward ^c	0	52	22	91	30	22
60–89	Upward	52	21	145	8	101	176
	Unchanged	479	467	386	432	419	347
	Downward	0	43	0	80	0	0
45–59	Upward	41	4	113	0	72	152
	Unchanged	198	175	126	138	128	66
	Downward	0	60	0	63	1	0
30–44	Upward	3	0	10	0	8	70
	Unchanged	101	68	83	65	82	58
	Downward	1	37	12	36	11	0
15–29	Upward	0	0	0	0	0	25
	Unchanged	38	29	35	30	36	41
	Downward	1	10	4	9	3	0
<15	Upward	0	0	0	0	0	6
	Unchanged	30	30	30	31	31	34
	Downward	0	0	0	0	0	0

Notes: ^aThe reclassification by the equation before the parentheses relative to the other one in parentheses; ^bupward to the higher GFR categories; ^cdownward to the lower GFR categories.

Abbreviations: GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; CMDRD, Chinese MDRD equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; Mayo, Mayo Clinic quadratic equation.

Table 4 The net reclassification improvement in risk of mortality

Equation comparisons	Appropriate move		Inappropriate move		NRI ^a	P-value
	Upward/survived	Downward/died	Downward/survived	Upward/died		
CMDRD (MDRD) ^b	(78/832+	1/218)	– (1/832	+18/218)	0.02	0.258
CKD-EPI (MDRD)	(24/832+	55/218)	– (147/832	+1/218)	0.10	0.004
Mayo (MDRD)	(227/832+	17/218)	– (21/832	+41/218)	0.14	<i>P</i> < 0.001
CKD-EPI (CMDRD)	(8/832+	71/218)	– (208/832	+0/218)	0.09	<i>P</i> < 0.001
Mayo (CMDRD)	(156/832+	18/218)	– (27/832	+25/218)	0.12	<i>P</i> < 0.001
Mayo (CKD-EPI)	(346/832+	5/218)	– (17/832	+83/218)	0.04	0.221

Notes: ^aNRI was calculated as follows: appropriate move [proportion of participants reclassified upward to a higher GFR category who survived + proportion of participants reclassified downward to a lower GFR category who died] – inappropriate move [proportion of participants reclassified downward to a lower GFR category who survived + proportion of participants reclassified upward to a higher GFR category who died]. The GFR was divided into six different categories, including >90, 60–89, 45–59, 30–44, 15–29, and <15 mL/minutes/1.73 m². The Z statistic was used to determine the significance of NRI; ^bthe NRI of the equation before the parentheses relative to the other one in parentheses.

Abbreviations: CMDRD, Chinese Modification of Diet in Renal Disease equation; MDRD, Modification of Diet in Renal Disease study equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; Mayo, Mayo Clinic quadratic equation; NRI, net reclassification improvement; GFR, glomerular filtration rate.

Discussion

The NHANES study has shown that there is a higher level of GFR and a lower prevalence of renal function impairment in the general population when using the CKD-EPI equation compared with the MDRD equation,¹⁹ but in the light of a recent study directed at the elderly, the result appeared to be the opposite for the elderly.²⁰ Similarly, we found in elderly Chinese that the order of the median GFR from high to low was the Mayo-GFR, CMDRD-GFR, MDRD-GFR, and EPI-GFR. The order of GFR < 60 mL/minute/1.73 m² prevalence from high to low was the CKD-EPI-GFR, MDRD-GFR, CMDRD-GFR, and Mayo-GFR. Previous trials with the general population as the study subjects mainly attributed the higher level of GFR and a lower prevalence of renal function impairment using the CKD-EPI equation to the subgroups at low risk for CKD (age < 60 years, women, and white subjects). For these subgroups, there were lower levels of GFR and a higher prevalence of renal function impairment according to the MDRD equation.²¹ Our study was aimed directly at the elderly Chinese with CAD, who tended to be older, male, and at high risk for renal function impairment.

Recent studies have shown that people at lower risk for renal function impairment, such as women, younger, and white subjects, were mainly reclassified to lower GFR categories using the CKD-EPI equation and had a lower risk of death, indicating that the CKD-EPI equation improved categorization concerning mortality compared with the MDRD equation.^{21–24} However, the better reclassification of the CKD-EPI was not validated by another study with a focus on the elderly.²⁵ In the current study, the AUC and NRI values showed that the prognostic abilities of the EPI-GFR and Mayo-GFR were far superior to the MDRD-GFR and CMDRD-GFR. Moreover, even without statistical

significance, the Mayo equation still categorized individuals more appropriately than the CKD-EPI equation and might better predict adverse outcomes.

Several studies, such as the Health, Aging, and Body Composition study, showed that a GFR < 60 mL/minute/1.73 m² compared with a GFR > 60 mL/minute/1.73 m², was a strong predictor of cardiovascular death.²⁶ However, Go et al²⁷ believed that a GFR < 45 mL/minute/1.73 m², rather than a GFR < 60 mL/minute/1.73 m², was the threshold below which all-cause mortality significantly increased. In addition, the Alberta Provincial Project for Outcomes Assessments in Coronary Heart Disease (APPROACH) Registry proposed that a GFR < 79 mL/minute/1.73 m², but not a GFR > 90 mL/minute/1.73 m², was the cut-off value for a significant increase in all-cause mortality.²⁸ In fact, all of the studies transformed the GFR to a categorical variable with the levels set in advance, compared the correlation of different categories with mortality, and selected one preset level as the cut-off point, which was limited by the subjective factor. Unlike those studies, the current study used the GFR as a continuous variable and defined the cut-off value with the ROC curve, showing stronger objectivity and accuracy, which demonstrated that even with the presence of better cut-off values, a GFR < 60 mL/minute/1.73 m² was still a significant predictor of mortality, independent of which equation was used. The National Kidney Foundation acknowledged that identifying subjects with impaired renal function based on the GFR, without reference to age, gender, race, and comorbidity, might lead to an inappropriate prognostic assessment of CKD.²⁹ For elderly Chinese patients with CAD, the current study demonstrated that the optimal cut-off values to predict a significant increase in mortality were set at 54.1 mL/minute/1.73 m² for the MDRD-GFR,

53.5 mL/minute/1.73 m² for the CMDRD-GFR, 48.0 mL/minute/1.73 m² for the CKD-EPI-GFR, and 57.4 mL/minute/1.73 m² for the Mayo-GFR.

To summarize, the prognostic abilities of the CKD-EPI and Mayo equations were significantly superior to the MDRD and CMDRD equations, and the Mayo equation had a mild, but not statistically significant superiority compared with the CKD-EPI equation in elderly Chinese patients with CAD. Although a GFR < 60 mL/minute/1.73 m² was still an independent predictor of high mortality independent of which equation was used, the optimal GFR cut-off values indicating a significant increase in mortality were set at 54.1 mL/minute/1.73 m² for the MDRD-GFR, 53.5 mL/minute/1.73 m² for the CMDRD-GFR, 48.0 mL/minute/1.73 m² for the CKD-EPI-GFR, and 57.4 mL/minute/1.73 m² for the Mayo-GFR.

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Disclosure

The authors report no conflicts of interest in this work.

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