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Associations between different eGFR estimating equations and mortality for CVD patients

A retrospective cohort study based on the NHANES database

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Abstract

To assess the associations of $eGFR_{CKD-EPI}$ (estimated glomerular filtration rate (eGFR) by chronic kidney disease epidemiology collaboration equation), $eGFR_{MDRD}$ (eGFR by modification of diet in renal disease), and serum creatinine (scr) on the death for American people diagnosed with cardiovascular disease (CVD) respectively, and to compare the predicted performance of $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and scr. A total of 63,078 participants who derived from the National Health and Nutrition Examination Survey (NHANES) database, were obtained in this retrospective cohort study, and collected the baseline characteristics all participants. The outcomes of our study were defined as death, and eGFR estimating equations was defined as $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and scr. Univariate and multivariate COX analysis were performed to assess the relationship. A subgroup analysis was conducted based on whether patients had anemia. Simultaneously, we also considered the predictive value of $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and scr in the risk of death. All patients were followed for at most 5-years. After excluded participants who did not meet the inclusion criteria and had missing information, the present study included 2419 participants ultimately, and were divided into alive group (n = 1800) and dead group (n = 619). The mortality rate for CVD patients in this study was approximately 25.59% at the end of follow-up. After adjustment for covariates, the result showed that participants with $eGFR_{CKD-EPI}$/$eGFR_{MDRD}$ < 30 mL/min/1.73 m^2 or 30 to 45 mL/min/1.73 m^2 had a higher risk of mortality. Similarly, participants with scr (Q4 ≥ 1.2) were associated with the increased risk of death. Additionally, $eGFR_{CKD-EPI}$ has a higher predictive value in 1-year, 3-years, and 5-years risk of death among patients with CVD than $eGFR_{MDRD}$ and scr. The lower level of eGFR was associated with higher risk of death among American population diagnosed with CVD, especially for non-anemic patients. Importantly, our study also displayed that CKD-EPI-based calculation equation of eGFR ($eGFR_{CKD-EPI}$) provided for a better predictive value than $eGFR_{MDRD}$ and scr in the risk of death.

Abbreviations: AUC = area under the curve, BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, CRP = C-reactive protein, CVD = cardiovascular disease, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, eGFRCKD-EPI = estimated glomerular filtration rate (eGFR) by chronic kidney disease epidemiology collaboration equation, HR = hazard ratio, MDRD = modification of diet in renal diseases, NHANES = National Health and Nutrition Examination Survey, PIR = poverty income ratio, ROC = receiver operator characteristic, SBP = systolic blood pressure, scr = serum creatinine.

Keywords: anemia, CVD, death, estimating equation, glomerular filtration rate

1. Introduction

Cardiovascular disease (CVD), as the leading cause of death worldwide, caused the number of deaths is also sustaining rise.[1,2] Of which chronic kidney disease (CKD) has been considered as an independent risk factor in patients with CVD.[3] Renal impairment in patients with CVD may manifest as a reduction of the estimated glomerular filtration rate (eGFR).[4] The inclusion of simple kidney biomarkers in clinical practice for CVD prevention is of great value.

Previous studies have point out that eGFR have been believed to be predictor for CVD death. In the study of a Chinese population-based retrospective cohort study, Fung et al, found that the risk of CVD events and mortality increases exponentially as eGFR decreases.[5] Additionally, Kim et al, also assessed the association of eGFR and CVD mortality among Korean adults aged ≥ 50 years, and the results demonstrated that the eGFR were associated independently with CVD mortality after adjusting covariates.[6] A determination of eGFR in everyday clinical practice is necessary. In recent decades, a number of equations based on creatinine levels have commonly been developed for eGFR,[7,8] and including chronic kidney disease epidemiology collaboration equation ($eGFR_{CKD-EPI}$),[9] and modification of diet in renal disease ($eGFR_{MDRD}$).[10] As far as

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The datasets generated during and/or analyzed during the current study are publicly available.

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Table 1

Characteristics of all participants.

Variables	Total (n = 2419)	Alive group (n = 1800)	Dead group (n = 619)	Statistics	P
Age (yr), mean ± SD	67.56 ± 12.89	65.41 ± 13.13	73.82 ± 9.77	$t = -16.82$	<.001
Gender, n (%)				$\chi^2 = 6.503$	.011
Male	1391 (57.50)	1008 (56.00)	383 (61.87)		
Female	1028 (42.50)	792 (44.00)	236 (38.13)		
Race, n (%)				$\chi^2 = 15.869$	.003
Mexican American	335 (13.85)	272 (15.11)	63 (10.18)		
Other Hispanic	118 (4.88)	96 (5.33)	22 (3.55)		
Non-Hispanic White	1463 (60.48)	1055 (58.61)	408 (65.91)		
Non-Hispanic Black	411 (16.99)	305 (16.94)	106 (17.12)		
Other race	92 (3.80)	72 (4.00)	20 (3.23)		
Educational level, n (%)				$Z = -1.977$	.048
Less than 9th grade	510 (21.08)	371 (20.61)	139 (22.46)		
9–11th grade	486 (20.09)	352 (19.56)	134 (21.65)		
High school	583 (24.10)	432 (24.00)	151 (24.39)		
Some colleges	534 (22.08)	408 (22.67)	126 (20.36)		
College graduate or above	306 (12.65)	237 (13.17)	69 (11.15)		
Marital status, n (%)				$\chi^2 = 78.369$	<.001
Married	1311 (54.20)	1031 (57.28)	280 (45.23)		
Widowed	553 (22.86)	334 (18.56)	219 (35.38)		
Divorced	282 (11.66)	215 (11.94)	67 (10.82)		
Separated	65 (2.69)	53 (2.94)	12 (1.94)		
Never married	136 (5.62)	104 (5.78)	32 (5.17)		
Living with partner	72 (2.98)	63 (3.50)	9 (1.45)		
Family PIR, M (Q_1, Q_3)	1.72 (1.04,3.29)	1.78 (1.03,3.51)	1.63 (1.07,2.64)	$Z = -2.523$	.012
BMI (kg/m^2), mean ± SD	29.69 ± 6.75	30.08 ± 6.68	28.56 ± 6.81	$t = 4.87$	<.001
SBP, mean ± SD	133.54 ± 22.80	132.65 ± 22.10	136.16 ± 24.55	$t = -3.15$	.002
DBP, mean ± SD	66.66 ± 16.00	68.21 ± 15.19	62.14 ± 17.40	$t = 7.74$	<.001
Alcohol drinks, n (%)				$\chi^2 = 0.036$	.849
Yes	1563 (64.61)	1165 (64.72)	398 (64.30)		
No	856 (35.39)	635 (35.28)	221 (35.70)		
Smoking, n (%)				$\chi^2 = 1.167$	.280
Yes	1476 (61.02)	1087 (60.39)	389 (62.84)		
No	943 (38.98)	713 (39.61)	230 (37.16)		
Hypertension, n (%)				$\chi^2 = 2.258$	.133
Yes	1721 (71.15)	1266 (70.33)	455 (73.51)		
No	698 (28.85)	534 (29.67)	164 (26.49)		
Diabetes mellitus, n (%)				$\chi^2 = 8.273$	.016
Yes	702 (29.02)	496 (27.56)	206 (33.28)		
No	1633 (67.51)	1244 (69.11)	389 (62.84)		
Borderline	84 (3.47)	60 (3.33)	24 (3.88)		
Anemia, n (%)				$\chi^2 = 36.710$	<.001
Yes	203 (8.39)	115 (6.39)	88 (14.22)		
No	2216 (91.61)	1685 (93.61)	531 (85.78)		
Vigorous activity, n (%)				$\chi^2 = 61.004$	<.001
Yes	172 (7.11)	162 (9.00)	10 (1.62)		
No	2072 (85.66)	1537 (85.39)	535 (86.43)		
Unable to do activity	175 (7.23)	101 (5.61)	74 (11.95)		
Moderate activity, n (%)				$\chi^2 = 64.532$	<.001
Yes	755 (31.21)	635 (35.28)	120 (19.39)		
No	1535 (63.46)	1090 (60.56)	445 (71.89)		
Unable to do activity	129 (5.33)	75 (4.17)	54 (8.72)		
HDL-cholesterol (mmol/L), M (Q_1, Q_3)	1.20 (1.00,1.48)	1.19 (1.01,1.47)	1.22 (0.98,1.50)	$Z = 0.405$	.685
Glucose (mmol/L), M (Q_1, Q_3)	5.50 (5.00,6.61)	5.44 (4.97,6.49)	5.61 (5.00,6.99)	$Z = 3.140$	.002
Creatinine (umol/L), M (Q_1, Q_3)	86.63 (70.70,106.08)	81.33 (68.95,98.12)	97.24 (79.56,132.60)	$Z = 12.430$	<.001
CRP (mg/dL), M (Q_1, Q_3)	0.29 (0.12,0.67)	0.27 (0.11,0.61)	0.43 (0.17,0.97)	$Z = 7.020$	<.001
Scr, M (Q_1, Q_3)	0.98 (0.80,1.20)	0.92 (0.78,1.11)	1.10 (0.90,1.50)	$Z = 12.430$	<.001
Scr group, n (%)				$Z = 11.722$	<.001
Q_1 (<0.799)	545 (22.53)	463 (25.72)	82 (13.25)		
Q_2 (0.799–0.980)	664 (27.45)	542 (30.11)	122 (19.71)		
Q_3 (0.980–1.200)	558 (23.07)	427 (23.72)	131 (21.16)		
Q_4 (≥1.2)	652 (26.95)	368 (20.44)	284 (45.88)		
$eGFR_{CKD-EPI}$, M (Q_1, Q_3)	74.86 (56.20,92.30)	79.76 (61.71,94.88)	60.47 (40.09,79.08)	$Z = -14.674$	<.001
$eGFR_{CKD-EPI}$ group (mL/min/1.73 m^2), n (%)				$Z = -14.276$	<.001
<30	120 (4.96)	42 (2.33)	78 (12.60)		
30–45	222 (9.18)	111 (6.17)	111 (17.93)		
45–60	361 (14.92)	246 (13.67)	115 (18.58)		
60–90	1042 (43.08)	809 (44.94)	233 (37.64)		
≥90	674 (27.86)	592 (32.89)	82 (13.25)		

(Continued)

Table 1

(Continued)

Variables	Total (n = 2419)	Alive group (n = 1800)	Dead group (n = 619)	Statistics	P
$eGFR_{MDRD}$, *M* (Q_1, Q_3)	74.44 (57.16,91.10)	77.79 (62.53,94.28)	62.34 (41.59,79.31)	$Z = -12.796$	<.001
$eGFR_{MDRD}$ group (mL/min/1.73 m^2), n (%)				$Z = -12.522$	<.001
<30	102 (4.22)	37 (2.06)	65 (10.50)		
30–45	217 (8.97)	105 (5.83)	112 (18.09)		
45–60	362 (14.96)	250 (13.89)	112 (18.09)		
60–90	1098 (45.39)	864 (48.00)	234 (37.80)		
≥90	640 (26.46)	544 (30.22)	96 (15.51)		

χ^2 = Chi-square test, BMI = body mass index, CRP = C-reactive protein, DBP = diastolic blood pressure, $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate (eGFR) by chronic kidney disease epidemiology collaboration equation, $eGFR_{MDRD}$ = eGFR by modification of diet in renal disease, HDL = high density lipoprotein, *M* (Q1, Q3) = median and quartile spacing, mean ± SD = mean ± standard deviation, PIR = poverty income ratio, SBP = systolic blood pressure, Scr = serum creatinine, *t* = *t* test, *Z* = Mann–Whitney *U* rank-sum test.

we know, the applicability of eGFR estimating equations in the death of American population with CVD remains unclear, moreover, there were few studies to focus on the association of eGFR and death of CVD for anemia people.

Herein, by using data from the National Health and Nutrition Examination Survey (NHANES) database, we aimed to explore the effect of $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and scr on the death for American people diagnosed with CVD respectively, and pay attention to the effects of $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and scr among anemia population, in addition to further compare the predicted performance of $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and scr.

2. Methods

2.1. Data sources and study eligibility criteria

The information of all CVD patients in the current study was extracted from NHANES database. As a cross-sectional survey of the National Center for Health Statistics, NHANES collects the information of participants by combining the way of interviews and physical examinations, aiming to assess the health and nutritional status of adults and children in the United States.[11] Participants were sampled via using a complex multistage probabilistic sampling method, to allow the results to be generalized to other populations.[12]

This retrospective cohort study used data of NHANES database from 1999 to 2014. A total of 63,078 participants were obtained in this present analysis. We only involved patients who were diagnosed with CVD and aged ≥ 18 years old. Simultaneously, we also excluded some patients who had missing information of creatinine or history of blood pressure. During follow-up period, we also excluded patients who were lost to follow-up. Due to these data were publicly available, this study did not require institutional review board approval of the Second Affiliated Hospital of Nanjing Medical University.

2.2. Data collection

The baseline characteristics all participants were collected as following: age, gender, race, educational level, marital status, family poverty income ratio (PIR), body mass index (BMI, kg/m^2), systolic blood pressure (SBP), diastolic blood pressure (DBP), alcohol drinks, smoking, hypertension, diabetes mellitus, anemia, vigorous activity, moderate activity, high density lipoprotein-cholesterol (mmol/L), glucose (mmol/L), creatinine (umol/L), C-reactive protein (CRP, mg/dL), serum creatinine (scr), the level of $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and scr.

$eGFR_{CKD-EPI}$ was defined as following[9]: $=141 \times \min(scr/\kappa, 1)^{\alpha} \times \max(scr/\kappa, 1)^{-1.029} \times 0.993^{age} \times 1.108$ (if female), where age is in years, scr is the serum creatinine level in mg/dL, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of scr/κ or 1, and max indicates the maximum of scr/κ or 1. Scr stands for serum creatinine (mg/dL). $eGFR_{MDRD}$ was calculated by using the modification of diet in renal diseases (MDRD) method: $186.3 \times (\text{serum creatinine}^{1.154}) \times (\text{age}^{0.203}) \times 0.742$ (if female).[10] Based on the different level, $eGFR_{CKD-EPI}$ and $eGFR_{MDRD}$ were divided into group: ≥90 mL/min/1.73 m^2, 60 to 90 mL/min/1.73 m^2, 45 to 60 mL/min/1.73 m^2, 30 to 45 mL/min/1.73 m^2, <30 mL/min/1.73 m^2. Scr group was based on quartile into 4 groups: Q1 (<0.799), Q2 (0.799–0.980), Q3 (0.980–1.200), Q4 (≥1.2).

2.3. Outcomes and follow-up

The outcomes of our study were defined as death. All patients were followed for at most 5-years, and follow-up was terminated once death occurred for CVD patients in this study. eGFR estimating equations was defined as $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and scr.

2.4. Statistical analysis

The measurement data of normal distribution was expressed by mean ± standard deviation (mean ± SD = mean ± standard deviation), *t* test was adopted for the comparison between 2 groups, and analysis of variance was used for the comparison between multiple groups. The measurement data of non-normal distribution was described by the median and quartile spacing, and comparison between 2 groups performed the Mann–Whitney *U* rank-sum test and between multiple groups adopted Kruskal–Wallis test. In addition, the enumeration data were shown via the number of cases and the composition ratio (n [%]), comparison between groups adopted Chi-square test.

In the current study, we performed the univariate COX analysis and multivariate COX analysis, to assess the effect of $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and scr on the death for patients diagnosed with CVD respectively, and focusing on the effects of $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and scr among anemia population. Three models were introduced, Model 1 was non-adjusted; Model 2 adjusted age and gender; Model 3 adjusted age, gender, race, marital status, family PIR, BMI, SBP, DBP, diabetes mellitus, vigorous activity, moderate activity, glucose, CRP. Simultaneously, we also considered the predictive value of $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and scr in 5-years risk of death among patients with CVD by the C-index and area under the curve (AUC) of receiver operator characteristic (ROC) curves. Hazard ratio (HR) and 95% confidence interval (CI) were calculated in the study. SAS software performed statistical analysis and plotted time-dependent ROC curves, and R4.0.3 software was used for drawing KM graph. $P < .05$ was considered statistically significant. Further, multiple Imputation (R: mice) was used to interpolate the missing value, and the sensitivity analysis after interpolation was displayed in Table S1, Supplemental Digital Content, http://links.lww.com/MD/H385.

Table 2

The univariate COX proportional hazard analysis of all patients characteristics.

Variables	β	S.E.	χ^2	*P*	HR	Lower	Upper
Age	0.061	0.004	186.215	<.001	1.06	1.05	1.07
Gender							
Male					Ref		
Female	–0.208	0.083	6.345	.012	0.81	0.69	0.95
Race							
Mexican American					Ref		
Other Hispanic	–0.009	0.248	0.001	.972	0.99	0.61	1.61
Non-Hispanic White	0.464	0.135	11.765	<.001	1.59	1.22	2.07
Non-Hispanic Black	0.390	0.159	6.022	.014	1.48	1.08	2.02
Other race	0.203	0.257	0.628	.428	1.23	0.74	2.03
Educational level							
Less than 9th grade					Ref		
9–11th grade	0.007	0.121	0.003	.956	1.01	0.79	1.28
High school	–0.056	0.118	0.231	.631	0.95	0.75	1.19
Some colleges	–0.156	0.123	1.599	.206	0.86	0.67	1.09
College graduate or above	–0.209	0.147	2.008	.156	0.81	0.61	1.08
Marital status							
Married					Ref		
Widowed	0.751	0.090	69.223	<.001	2.12	1.78	2.53
Divorced	0.104	0.136	0.588	.443	1.11	0.85	1.45
Separated	–0.165	0.295	0.314	.575	0.85	0.48	1.51
Never married	0.093	0.187	0.250	.617	1.10	0.76	1.58
Living with partner	–0.603	0.339	3.166	.075	0.55	0.28	1.06
Family PIR	–0.111	0.028	15.374	<.001	0.89	0.85	0.95
BMI	–0.033	0.007	24.360	<.001	0.97	0.95	0.98
SBP	0.005	0.002	10.179	.001	1.01	1.01	1.01
DBP	–0.018	0.002	72.490	<.001	0.98	0.98	0.99
Alcohol drinks							
Yes					Ref		
No	0.025	0.084	0.092	.762	1.03	0.87	1.21
Smoking							
Yes					Ref		
No	–0.086	0.083	1.070	.301	0.92	0.78	1.08
Hypertension							
Yes					Ref		
No	–0.136	0.091	2.242	.134	0.87	0.73	1.04
Diabetes mellitus							
Yes					Ref		
No	–0.248	0.086	8.296	.004	0.78	0.66	0.92
Borderline	–0.026	0.216	0.014	.904	0.97	0.64	1.49
Anemia							
Yes					Ref		
No	–0.710	0.115	38.048	<.001	0.49	0.39	0.62
Vigorous activity							
Yes					Ref		
No	1.601	0.319	25.170	<.001	4.96	2.65	9.27
Unable to do activity	2.222	0.337	43.494	<.001	9.23	4.77	17.86
Moderate activity							
Yes					Ref		
No	0.674	0.103	42.891	<.001	1.96	1.60	2.40
Unable to do activity	1.137	0.164	48.077	<.001	3.12	2.26	4.30
HDL-cholesterol	0.139	0.095	2.147	.143	1.15	0.95	1.38
Glucose	0.044	0.012	14.419	<.001	1.05	1.02	1.07
Creatinine	0.002	0.000	78.915	<.001	1.01	1.01	1.01
CRP	0.148	0.017	78.073	<.001	1.16	1.12	1.20
$eGFR_{CKD-EPI}$ group							
<30	2.136	0.159	181.536	<.001	8.47	6.20	11.55
30–45	1.670	0.146	131.187	<.001	5.31	3.99	7.07
45–60	1.110	0.145	59.003	<.001	3.04	2.29	4.03
60–90	0.671	0.128	27.308	<.001	1.96	1.52	2.52
≥90					Ref		
Scr group							
Q_1 (<0.799)					Ref		
Q_2 (0.799–0.980)	0.219	0.143	2.348	.125	1.24	0.94	1.65
Q_3 (0.980–1.200)	0.495	0.141	12.371	<.001	1.64	1.25	2.16
Q_4 (≥1.2)	1.272	0.125	102.828	<.001	3.57	2.79	4.56
$eGFR_{MDRD}$ group							
<30	1.860	0.161	133.614	<.001	6.43	4.69	8.81
30–45	1.488	0.139	114.239	<.001	4.43	3.37	5.82

(Continued)

Table 2

(Continued)

Variables	β	S.E.	χ^2	*P*	HR	Lower	Upper
45–60	0.847	0.139	37.030	<.001	2.33	1.78	3.06
60–90	0.386	0.121	10.119	.001	1.47	1.16	1.86
≥90					Ref		

BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, DBP = diastolic blood pressure, $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate (eGFR) by chronic kidney disease epidemiology collaboration equation, $eGFR_{MDRD}$ = eGFR by modification of diet in renal disease, HDL = high density lipoprotein, HR = hazard ratio, PIR = poverty income ratio, SBP = systolic blood pressure, Scr = serum creatinine.

Table 3

Associations between eGFR estimating equations and mortality for CVD patients.

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
$eGFR_{CKD-EPI}$						
≥90	Ref		Ref		Ref	
60–90	1.96 (1.52–2.52)	<.001	1.08 (0.82–1.41)	.579	1.08 (0.82–1.43)	.566
45–60	3.04 (2.29–4.03)	<.001	1.32 (0.97–1.81)	.079	1.28 (0.93–1.76)	.131
30–45	5.31 (3.99–7.07)	<.001	2.30 (1.68–3.15)	<.001	1.98 (1.43–2.74)	<.001
<30	8.47 (6.20–11.55)	<.001	4.51 (3.25–6.26)	<.001	3.35 (2.36–4.77)	<.001
$eGFR_{MDRD}$						
≥90	Ref		Ref		Ref	
60–90	1.47 (1.16–1.87)	.002	0.95 (0.74–1.21)	.656	0.94 (0.73–1.21)	.631
45–60	2.33 (1.78–3.06)	<.001	1.23 (0.92–1.64)	.156	1.19 (0.88–1.59)	.255
30–45	4.43 (3.37–5.82)	<.001	2.28 (1.71–3.03)	<.001	1.89 (1.40–2.56)	<.001
<30	6.43 (4.67–8.81)	<.001	4.22 (3.05–5.84)	<.001	3.08 (2.17–4.38)	<.001
Scr						
Q_1 (<0.799)	Ref		Ref		Ref	
Q_2 (0.799–0.980)	1.25 (0.94–1.65)	.126	1.05 (0.79–1.39)	.743	1.02 (0.76–1.36)	.905
Q_3 (0.980–1.200)	1.64 (1.25–2.16)	<.001	1.19 (0.89–1.58)	.250	1.10 (0.82–1.47)	.537
Q_4 (≥1.2)	3.57 (2.79–4.56)	<.001	2.24 (1.73–2.93)	<.001	1.86 (1.42–2.45)	<.001

Model 1: did not adjust any variables; Model 2: adjusted age and gender; Model 3: adjusted age, gender, race, marital status, family poverty income ratio (PIR), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), diabetes mellitus, vigorous activity, moderate activity, glucose, C-reactive protein (CRP).
CI = confidence interval, CVD = cardiovascular disease, $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate (eGFR) by chronic kidney disease epidemiology collaboration equation, $eGFR_{MDRD}$ = eGFR by modification of diet in renal disease, HR = hazard ratio, Scr = serum creatinine.

Table 4

Associations between eGFR estimating equations and mortality based on CVD patients with anemia.

	Anemia population		Non-anemia population	
	HR (95% CI)	*P*	HR (95% CI)	*P*
$eGFR_{CKD-EPI}$				
≥90	Ref		Ref	
60–90	1.03 (0.35–3.08)	.957	1.06 (0.80–1.42)	.685
45–60	0.70 (0.20–2.49)	.581	1.32 (0.95–1.85)	.102
30–45	1.77 (0.54–5.83)	.350	1.97 (1.39–2.78)	<.001
<30	2.30 (0.76–7.01)	.142	3.68 (2.50–5.43)	<.001
$eGFR_{MDRD}$				
≥90	Ref		Ref	
60–90	0.88 (0.33–2.35)	.797	0.94 (0.73–1.22)	.640
45–60	0.74 (0.25–2.17)	.579	1.24 (0.91–1.69)	.170
30–45	1.87 (0.67–5.22)	.234	1.86 (1.35–2.57)	<.001
<30	2.05 (0.76–5.55)	.159	3.60 (2.42–5.34)	<.001
Scr				
Q_1 (<0.799)	Ref		Ref	
Q_2 (0.799–0.980)	0.69 (0.25–1.87)	.460	1.05 (0.78–1.42)	.762
Q_3 (0.980–1.200)	1.21 (0.46–3.16)	.704	1.08 (0.89–1.47)	.648
Q_4 (≥1.2)	1.66 (0.71–3.86)	.241	1.89 (0.41–2.53)	<.001

Model 1: did not adjust any variables; Model 2: adjusted age and gender; Model 3: adjusted age, gender, race, marital status, family poverty income ratio (PIR), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), diabetes mellitus, vigorous activity, moderate activity, glucose, C-reactive protein (CRP).
CI = confidence interval, CVD = cardiovascular disease, $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate (eGFR) by chronic kidney disease epidemiology collaboration equation, $eGFR_{MDRD}$ = eGFR by modification of diet in renal disease, HR = hazard ratio, Scr = serum creatinine.

3. Results

3.1. Demographics of participants

Of the 63,078 participants initially enrolled, the present study excluded 10,247 patients who were < 18 years old, 36,871 who were non-CVD patients, 2167 patients who had missing information of creatinine or history of blood pressure, and 11,374 patients who were lost to follow-up during follow-up period. Ultimately, there were 2419 participants were included in the present analyses, and these patients were divided into alive group (n = 1800) and dead group (n = 619). The mortality rate for CVD patients in this study was approximately 25.59% at the end of follow-up. Detailed demographic and clinical characteristics of all participants was given in Table 1.

3.2. Associations between eGFR estimating equations and mortality for CVD patients

As shown in Table 2, the result of univariate COX analysis indicated that some variables were statistically difference, including age, gender, marital status, family PIR, BMI, SBP, DBP, diabetes mellitus, anemia, vigorous activity, moderate activity, glucose, creatinine, CRP and so on. Of note, when adjusted some covariates which have statistically difference (Table 3), participants with $eGFR_{CKD\text{-}EPI}$ < 30 mL/min/1.73 m^2 (HR = 3.35, 95%CI: 2.36–4.77) or 30 to 45 mL/min/1.73 m^2 (HR = 1.98, 95%CI: 1.43–2.74) had a higher risk of mortality, compared to participants with $eGFR_{CKD\text{-}EPI}$ ≥ 90 mL/min/1.73 m^2 (Model 3). Similarly, compared to participants with $eGFR_{MDRD}$ ≥ 90 mL/min/1.73 m^2 (Model 3), CVD patients with $eGFR_{MDRD}$ < 30 mL/min/1.73 m^2 (HR = 3.08, 95%CI: 2.17–4.38) or 30 to 45 mL/min/1.73 m^2 (HR = 1.89, 95%CI: 1.40–2.56) were associated with a higher risk of mortality. Scr with Q4 (≥1.2) had 0.86-fold increased risk of death than CVD patients with Q1 (<0.799). Moreover, we also explored the associations between eGFR estimating equations and mortality based on the CVD patients with anemia. The result hinted that (Table 4), with respect to CVD patients with non-anemia, lower level of $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$ was associated with the higher risk of death, and scr with Q4 (≥1.2) had also an increased risk of death than patients with Q1 (<0.799). Interestingly, the relationship between $eGFR_{CKD\text{-}EPI}$, $eGFR_{MDRD,}$ scr and the risk of death was no longer statistically significant among CVD patients with anemia ($P > .05$).

3.3. Predictive value of eGFR estimating equations for mortality among CVD patients

More importantly, we identified the eGFR equation best correlated with the risk of death among patients with CVD in the present study. The C-index of $eGFR_{CKD\text{-}EPI}$ was 0.663 (95%CI: 0.643–0.683), higher than $eGFR_{MDRD}$ (C-index = 0.642, 95%CI: 0.620–0.664), and scr (C-index = 0.637, 95%CI: 0.615–0.659) (Table 5), which indicated that $eGFR_{CKD\text{-}EPI}$ has a higher predictive value for death than $eGFR_{MDRD}$ and Scr among CVD patients. Likewise, Table 6 also manifests that $eGFR_{CKD\text{-}EPI}$ has a higher predictive value in 1-year, 3-years, and 5-years risk of death among patients with CVD than $eGFR_{MDRD}$ and Scr. The time dependence ROC curve for eGFR estimating equations to predict death of CVD patients was shown in Figure 1.

Table 5

Predictive value of eGFR for mortality.

	C index (95%CI)	*Z*	*P*
$eGFR_{CKD\text{-}EPI}$	0.663 (0.643–0.683)	2.018	.044
$eGFR_{MDRD}$	0.642 (0.620–0.664)	0.643	.520
Scr	0.637 (0.615–0.659)	Ref	

CI = confidence interval, $eGFR_{CKD\text{-}EPI}$ = estimated glomerular filtration rate (eGFR) by chronic kidney disease epidemiology collaboration equation, $eGFR_{MDRD}$ = eGFR by modification of diet in renal disease, Scr = serum creatinine.

Table 6

Predictive value of eGFR for mortality at 1-yr, 3-yr, and 5-yr.

	AUC (95%CI)		
	1-yr	3-yr	5-yr
$eGFR_{CKD\text{-}EPI}$	0.735 (0.688–0.781)	0.692 (0.664–0.720)	0.682 (0.658–0.705)
$eGFR_{MDRD}$	0.718 (0.669–0.768)	0.662 (0.633–0.691)	0.658 (0.634–0.683)
Scr	0.699 (0.650–0.748)	0.658 (0.629–0.687)	0.653 (0.628–0.677)

AUC = area under the curve, CI = confidence interval, $eGFR_{CKD\text{-}EPI}$ = estimated glomerular filtration rate (eGFR) by chronic kidney disease epidemiology collaboration equation, $eGFR_{MDRD}$ = eGFR by modification of diet in renal disease, Scr = serum creatinine.

4. Discussion

In this cohort of American population diagnosed with CVD, lower level of eGFR was associated with higher risk of death for CVD patients after adjustment for covariates, especially for non-anemic patients. Additionally, our study also illustrated that $eGFR_{CKD\text{-}EPI}$ had a better predictive value than $eGFR_{MDRD}$ and scr in terms of risk of death.

To our knowledge, this study is the first to examine the association of eGFR equations and mortality in an American population diagnosed with CVD so far. Previous studies have proposed the prognostic role of eGFR changes on the CVD mortality,[13,14] which was consistent with the result of our study. Muntner et al, reported that after adjusting for covariates, reduced $eGFR_{CKD\text{-}EPI}$ was related to an increased risk for mortality among people ≥ 45 years of age in the United States,[15] but this study used only one way to estimate GFR, and their study only considered the general population aged > 45 years old. In the present study, after adjusting some covariates, the findings displayed that a lower level of eGFR was associated with higher risk of death for CVD patients. Some plausible reasons can be used to explain these associations: firstly, when there were a reduced eGFR, CVD patients seems to have more serious risk factors (such as smoking, hypertension, diabetes mellitus, and so on), which increased the risk of death.[16] Secondly, published work pointed out that a reduced eGFR was associated with increased extracellular calcium and phosphorus concentrations, which might lead to vascular calcification, thereby increasing the risk of death in CVD patients.[6,17] Anemia was closely related to eGFR decline and the severe complications of CVD,[18,19] suggesting that the role of anemia should be considered when evaluating the relationship of eGFR level and the risk of death in patients with CVD. Therefore, we focusing on the CVD population with anemia. For non-anemic CVD patients, the association of lower level of eGFR and higher risk of death was stronger, which also suggested that we should pay more attention to the level of eGFR of non-anemic CVD patients.

Accurate measurement and estimation of GFR are important aspects in renal function diagnosis, evaluation of its severity and rate of progression, and appropriate management. Despite recognized deficiencies, eGFR based on the level of serum creatinine would remain the basis for renal function assessment.[20] Assessing the accuracy and predictive performance of eGFR from serum creatinine by using equations is of great value for public health and clinical care. Our study adopted 3 equations to eGFR based on the level of serum creatinine: $eGFR_{CKD\text{-}EPI}$, $eGFR_{MDRD}$, and scr. The result has indicated that the $eGFR_{CKD\text{-}EPI}$ equation provides a better predictive performance in risk of death for CVD patients compared to $eGFR_{MDRD}$, and scr. Not only that, similar results were found for 1-year, 3-years and 5-years risk of death.

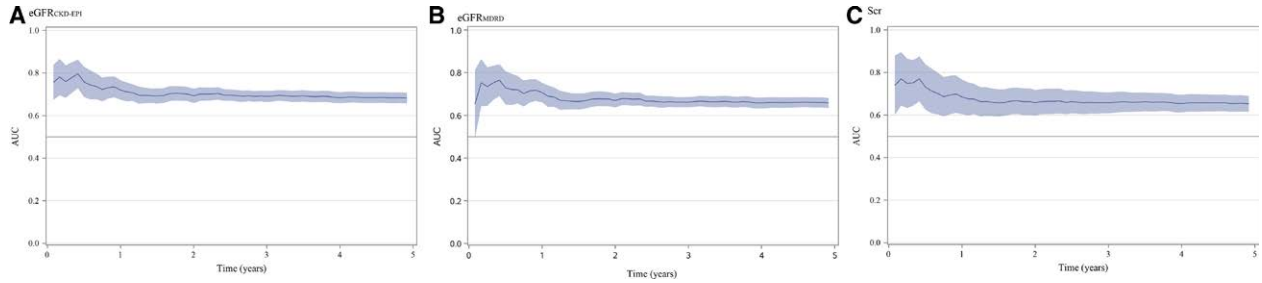

Figure 1 . The time dependence ROC curve for eGFR estimating equations to predict death of CVD. CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, ROC = receiver operator characteristic.

Some strengths of our study should be pointed. Firstly, previous literatures only calculated AUC without considering the effect of time. In our study, the survival time of patients was considered, C index was calculated and time-dependent AUC curve was drawn. Secondly, several studies have shown that CRP has an effect on the risk of death, but they have not adjusted for this measure as a covariate. Whereas our study adjusted for CRP as an important covariate. Finally, we performed a subgroup analysis based on the presence or absence of anemia in the population, a detailed analysis of the relationship between eGFR estimating equations and mortality is more applicable to non-anemic CVD patients. However, the limitations of this study cannot be ignored. Because of all data of this study derived from the NHANES database, we could not collect the information of cystatin C, and eGFR based on the level of cystatin C cannot therefore be obtained. Besides, we excluded some subjects who had the missing information, and we cannot be sure whether these participants affected the result of this study. More studies should be performed in the future.

5. Conclusion

In summary, this study has concluded that lower level of eGFR was associated with higher risk of death among American population diagnosed with CVD, especially for non-anemic patients. Importantly, our study also displayed that CKD-EPI-based calculation equation of eGFR ($eGFR_{CKD-EPI}$) provided for a better predictive value than $eGFR_{MDRD}$ and scr in terms of risk of death.

Author contributions

Zuhong Zhang, Maofang Zhu and Haiyan Zhang designed the study. Zuhong Zhang wrote the manuscript. Zuhong Zhang, Maofang Zhu and Zheng Wang collected, analyzed and interpreted the data. Haiyan Zhang critically reviewed, edited and approved the manuscript. All authors read and approved the final manuscript.

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