Predictive value of creatinine-based equations of kidney function in the long-term prognosis of United Arab Emirates patients

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Abstract

Objectives

Chronic kidney disease (CKD) is an independent predictor of mortality. Several creatinine-based equations are used to assess the estimated glomerular filtration rate or creatinine clearance and mortality prediction in various ethnic populations. Similarly, renal insufficiency is associated with poor prognosis among United Arab Emirates (UAE) nationals with cardiovascular disease (CVD) risk factors. However, the equation that best assesses prognosis among these patients is unknown. This study aimed to compare the prognostic abilities of different creatinine-based equations of kidney function for predicting all-cause mortality in UAE nationals with vascular comorbidities.

Methods

This retrospective observational study analyzed 1,186 patients (54% men) with CVD risk factors. Multivariable Cox regression analysis was used to evaluate the associations of categorical renal function stages with all-cause mortality. Measures of performance in each equation assessed with respect to all-cause mortality were evaluated and compared to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation by calculating the *C*-index, net reclassification index (NRI), and integrated discrimination index (IDI).

Results

Over a median follow-up of 8.9 years, the cumulative incidence of all-cause mortality was 9.4% (n = 112). After multivariable adjustment, the discriminative ability for all-cause mortality was significantly higher in the body surface area-adjusted Cockcroft-Gault (BSA-CG) formula than in the CKD-EPI equation (*C*-indices: 0.869 vs. 0.861, respectively, *P* = 0.037). NRI was significantly positive and favored the BSA-CG formula (0.54; 95% confidence interval, 0.35–0.64) compared to the CKD-EPI equation.

Conclusions

Our findings suggest that the BSA-CG equation may have the potential to slightly improve mortality prediction compared to the CKD-EPI equation in UAE nationals with vascular risk. Further large multicenter studies are warranted to confirm our findings.

Abbreviations: DM = diabetes mellitus, HTN = hypertension, CKD = chronic kidney disease, CVD = cardiovascular disease, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, TC = total cholesterol, TG = triglyceride, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, HbA1c = glycosylated

hemoglobin A1c, SCr = serum creatinine, eGFR = estimated glomerular filtration, CrCl = creatinine clearance, MDRD = Modification of Diet in Renal Disease Study, MCQ = Mayo Clinic Quadratic, FAS = Full Age Spectrum, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, CG = Cockcroft-Gault, ID/MS = isotope dilution mass spectrometry, NRI = Net Reclassification Indices, IDI = Integrated Discrimination Increment, SD = standard deviation, HR = hazard ratio, CI = confidence interval, IQR = interquartile range, BSA = body surface area, UAE = United Arab Emirates.

Keywords: cardiovascular disease, chronic kidney disease, renal function, mortality, United Arab Emirates

INTRODUCTION

Chronic kidney disease (CKD) is an independent risk factor for death, exhibiting an exponential relationship between the severity of renal impairment and mortality risk [1]. Additionally, CKD is often comorbid with known cardiovascular disease (CVD) risk factors [2–4], and patients with a combination of these conditions are at even higher risk of death [5]. Reducing the risk of premature mortality is a primary goal of clinicians; therefore, utilizing renal function for prognosis and risk stratification is of crucial importance at both an individual and population level.

Following its rapid economic development, the United Arab Emirates (UAE) has experienced a dramatic rise in CKD-related deaths [6]. Furthermore, a recent study among UAE nationals showed that renal insufficiency is associated with poor prognosis [7].

In the age of precision medicine, risk stratification and mortality prediction in at-risk populations are imperative for implementing personalized interventions and preventive measures

in a more evidence-based manner. Over the past decades, several creatinine-based equations have been developed to serve three important functions: to diagnose and classify CKD, to guide dose adjustment of medications, and to assess overall prognosis [8–10]. Equations such as the Modification of Diet in Renal Disease Study (MDRD) [11], the Mayo Clinic Quadratic (MCQ) equation [12], the Full Age Spectrum (FAS) equation [13], and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14] estimate glomerular filtration rate (eGFR), while the Cockcroft-Gault (CG) equation estimates creatinine clearance (CrCl) [15].

Current guidelines recommend the CKD-EPI equation as the most accurate method for diagnosing and staging CKD across multiple ethnicities [10,16]. The original CG formula estimates CrCl (and not GFR) and, therefore, has been found to overestimate GFR in younger and healthier populations but underestimate it in older populations [17,18]. However, the body surface area (BSA)-adjusted CG (BSA-CG) formula has been shown to be more accurate in estimating renal function compared with the original CG equation [19]. As such, the BSA-CG formula is still widely used in pharmacokinetic trials and in clinical practice [20–23].

The differential performance of these equations in the prediction of mortality has been previously assessed in multiple ethnic populations with vascular comorbidities [24–29]. In two recent European studies, the CG formula was found to have better accuracy in predicting mortality in patients with vascular risk compared with the CKD-EPI and MDRD equations [26,28]. While, among Chinese patients with diabetes, the CKD-EPI equation showed better prognostic value than the MDRD formula [24]. However, the creatinine-based equation of choice for predicting adverse prognosis and risk estimation among individuals of Arab descent remain unclear. Therefore, the aim of this study was to investigate and compare the long-term prognostic

abilities of several widely used creatinine-based equations in predicting mortality among UAE nationals with CVD risk.

METHODS

A retrospective cohort study design was employed to evaluate our research hypothesis by analyzing data from the electronic medical records of the outpatient clinics of Tawam Hospital in Al Ain, United Arab Emirates (UAE). We enrolled consecutive Emirati patients aged ≥ 18 years from April 1, 2008, to December 31, 2008, who had one of the following baseline conditions: a history of dyslipidemia, smoking, CVD, systolic blood pressure (SBP) ≥ 120 mmHg, diastolic blood pressure (DBP) ≥ 80 mmHg, serum glycated hemoglobin (HbA1c) level ≥ 5.7%, body mass index (BMI) ≥ 25 kg/m^2, and receiving antidiabetic or antihypertensive medications. Data were collected at the baseline visits in 2008 and at follow-up visits until September 30, 2018. Patients who had been receiving dialysis at baseline or those who underwent kidney transplant were excluded, due to potential inaccuracies in creatinine clearance estimation. In addition, patients with incomplete data on height, weight, and serum creatinine levels, and those without a follow-up clinic visit other than the baseline visit were also excluded.

The study protocol was approved by the institutional review board of Tawam Hospital and the UAE University (IRR536/17), and the requirement for informed consent was waived.

Clinical assessment

Sociodemographic data collected at baseline included age, sex, and history of smoking. Anthropometric information included height, weight, SBP, and DBP. Laboratory parameters included HbA1c, serum triglyceride (TG), serum low-density lipoprotein-cholesterol (LDL-C),

serum high-density lipoprotein-cholesterol (HDL-C), serum total cholesterol (TC), and serum creatinine (SCr) levels. Pharmacological treatment included the use of antihypertensive agents, lipid-lowering medications, and antidiabetic drugs.

All laboratory tests were performed at Tawam Hospital. SCr levels were assayed using the kinetic Jaffé method on the Synchron Clinical System (UniCel DxC-800; Beckman Coulter, Inc., Fullerton, CA). The Jaffé method offers traceability and calibration to a reference method, i.e., isotope dilution mass spectrometry (ID/MS). The manufacturer's suggested reference ranges for SCr level were 53–115 µmol/L (0.60–1.30 mg/dL) and 58–96 µmol/L (0.66–1.09 mg/dL) for men and women, respectively.

Assessment of eGFR and CrCl

In our study, eGFR and CrCl values were determined based on SCr (µmol/L), height (cm), weight (kg), and age (years), using the CKD-EPI [14], ID/MS-traceable version of the MDRD [11], CG [15], MCQ [12], and FAS equations [13] (Supplemental Table 1). The CG equation, which assessed CrCl that was not expressed by the unit (mL/min/1.73 m^2), was adjusted by multiplying the obtained values with 1.73 m^2 and dividing the products by the patients' BSA (BSA-CG) [19]. BSA was calculated using the DuBois formula [30]:

$0.007184 \times \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725}$

Table 1. Comparison of the patients' baseline characteristics according to all-cause mortality.

Characteristics	**Total (*n* = 1186)**	**Survivors (*n* = 1074)**	**Deceased (*n* = 112)**	***P*-value[a]**
Age (years), mean ± SD	52.4 ± 15.6	50.8 ± 15.0	67.8 ± 11.4	<0.001

Age (years), n (%)				
≤ 39	280 (23.6)	275 (25.6)	5 (4.5)	<0.001
40–54	334 (28.2)	326 (30.4)	8 (7.1)	
55–64	277 (23.4)	260 (24.2)	17 (15.2)	
≥ 65	295 (24.9)	213 (19.8)	82 (73.2)	
Men, n (%)	641 (54.0)	565 (52.6)	76 (67.9)	0.002
Comorbidities, n (%)				
Smoking history	227 (19.1)	199 (18.5)	28 (25.0)	0.102
Obesity	525 (44.3)	491 (45.7)	34 (30.4)	0.002
DM	570 (48.1)	489 (45.5)	81 (72.3)	<0.001
HTN	794 (66.9)	697 (64.9)	97 (86.6)	<0.001
Dyslipidemia	960 (80.9)	864 (80.4)	96 (85.7)	0.206
CVD	197 (16.6)	140 (13.0)	57 (50.9)	<0.001
Cancer	75 (6.3)	57 (5.3)	18 (16.1)	<0.001
Renal function				
SCr (μmol/L), median (IQR)	69.00 (56.00–84.25)	67.00 (55.00–81.00)	93.00 (70.25–125.25)	<0.001
SCr (mg/dL), median (IQR)	0.78 (0.63–0.95)	0.76 (0.62–0.92)	1.05 (0.79–1.42)	<0.001
CKD-EPI (mL/min/1.73 m^2), mean ± SD	94.89 ± 23.55	97.82 ± 21.39	66.76 ± 24.85	<0.001
MDRD (mL/min/1.73 m^2), mean ± SD	96.06 ± 31.57	98.90 ± 30.02	68.74 ± 33.12	<0.001

BSA-CG (mL/min/1.73 m^2), mean ± SD	112.02 ± 44.22	116.85 ± 42.64	65.75 ± 30.27	<0.001
MCQ (mL/min/1.73 m^2), mean ± SD	104.07 ± 23.51	106.80 ± 21.27	77.90 ± 27.70	<0.001
FAS (mL/min/1.73 m^2), mean ± SD	97.33 ± 32.30	100.80 ± 30.81	64.00 ± 26.87	<0.001

BSA-CG: body surface area-adjusted Cockcroft-Gault; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CVD: cardiovascular disease; DM: diabetes mellitus; FAS: Full Age Spectrum; HTN: hypertension; IQR: interquartile range; MCQ: Mayo Clinic Quadratic; MDRD: Modification of Diet in Renal Disease Study; SCr: serum creatinine; SD: standard deviation.

[a]The independent-samples t-test was used to calculate the *P*-values for continuous variables, and Fisher's exact test (two-tailed) for categorical variables. The Mann-Whitney U test was used to compare the median values of SCr levels.

The patients were classified according to their eGFR and CrCl values into CKD stages as per the National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines: stage 1, eGFR ≥ 90; stage 2, eGFR 60 to 89.99; stage 3a, eGFR 45 to 59.99; stage 3b, eGFR 30 to 44.99; stage 4, eGFR 15 to 29.99, and stage 5, eGFR < 15 in mL/min/1.73 m^2 [10].

Definitions of clinical and outcome variables

Hypertension (HTN) was defined by SBP values ≥ 140 mm Hg, or DBP ≥ 90 mm Hg, or by the use of antihypertensive medications [31]. Dyslipidemia was defined by one or more of the following: HDL-C < 1.03 mmol/L, TC ≥ 5.17 mmol/L, LDL-C ≥ 3.36 mmol/L, TG ≥ 1.69 mmol/L, or documented treatment with lipid-lowering drugs [32]. Patients receiving antidiabetic

medications or with an HbA1c level of ≥ 6.5% were considered to have type 2 diabetes (DM) [33]. Smoking history was considered positive if there was a current habit or past history of using tobacco products. Obesity was defined as BMI ≥ 30 kg/m^2. History of CVD was defined as a documented diagnosis of peripheral arterial disease, stroke, or coronary artery disease. Patients were considered as having a history of cancer if they had an established diagnosis of malignancy of any type. The primary outcome, all-cause mortality, was defined as death from any cause and was confirmed by review of death certificates and clinical records.

Statistical Analyses

Data were expressed as mean ± standard deviation (SD), as percentage, or as median [interquartile range (IQR)]. The baseline characteristics of deceased and alive subjects were compared using Fisher's exact test (two-tailed) for categorical variables, the independent samples t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables.

The univariable Kaplan Meier survival analysis, along with the log-rank test, was used to compare the survival functions across different CKD stages for each eGFR and CrCl equation. Univariable and multivariable Cox proportional hazards models were used to estimate the hazard ratios (HR) for all-cause mortality of the different eGFR and CrCl equations. To reduce the effect of other confounding variables on mortality, HRs were adjusted for sex, age (categories), CVD, DM, HTN, history of smoking, dyslipidemia, obesity, and cancer. The proportional hazards assumption was evaluated using log-log plots which were not significant. Multi-collinearity was assessed by examining the tolerance, and values > 0.2 indicated an absence of

multi-collinearity within the survival models. The results are reported as hazard ratios (HRs) and 95% confidence interval (CIs).

The prognostic discrimination of each eGFR and CrCl estimate in predicting all-cause mortality was tested by calculating the *C*-indices using the "survival" package in R software [34]. A *C*-index ranges from 0.5 to 1, with a value of 1 considered as perfect discrimination. The *C*-indices from each eGFR and CrCl equation were compared with the CKD-EPI equation using the "CompareC" package in R [35]. A larger increase in the *C*-index suggested better discriminatory value. Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were calculated to compare the predictive accuracy of CKD stage estimates between each eGFR and CrCl equation and the CKD-EPI formula with respect to all-cause mortality. The IDI and NRI assess the ability of a given model to appropriately or inappropriately reclassify patients into lower or higher levels of risk as compared with another model [36]. IDI and NRI were analyzed using the package "survIDINRI" in R [37].

All statistical analyses were performed using R software version 3.5.2 (The R Foundation, Vienna, Austria) and IBM®SPSS® software, version 25 (IBM Corporation, Armonk, NY, USA). Two-tailed *P*-values < 0.05 were considered statistically significant.

RESULTS

A total of 1,216 patients met the inclusion criteria. Of these, the following patients were excluded: 16 had missing values on one or more baseline variables required to estimate eGFR and CrCl (SCr, height, or weight), 10 had received a kidney transplant or had been receiving dialysis, and four patients did not have a follow-up clinic visit other than the baseline visit. The baseline characteristics of the remaining 1,186 patients included in the analyses are presented in

Table 1. With over a median follow-up of 8.9 years (IQR, 7.8 to 9.6 years), there were 112 deaths (9.4%) in the entire cohort. Of these deaths, 44 (39.3%) were due to coronary heart disease and stroke. At baseline, the mean age of the population was 52.4 ± 15.6 years, of which 54% were men. Almost half of the cohort had DM, and approximately two-thirds of patients had HTN. Approximately 81% had dyslipidemia and nearly 17% had CVD at baseline. Approximately 10% of patients were categorized as CKD stages 3–5 by the CKD-EPI formula. Those who died over the follow-up period were older at baseline; were more likely to be men; more frequently had a history of DM, HTN, CVD, and cancer; but less frequently had a history of obesity than survivors. As expected, those who died during follow-up had lower eGFR and CrCl values than survivors as calculated by all the creatinine-based equations at baseline.

Unadjusted long-term Kaplan-Meier survival curves of the eGFR and CrCl equations are presented in Fig 1. The survival distributions of all equations were significantly different (log-rank test, $P < 0.001$). However, the CKD stages diverged more noticeably with the BSA-CG equation (higher Chi^2 values). In the adjusted Cox regression analyses, all five eGFR and CrCl equations were significantly associated with all-cause mortality for the higher-severity renal function stages (CKD stages ≥ 3) compared to CKD stage 1 (reference category) (Table 2).

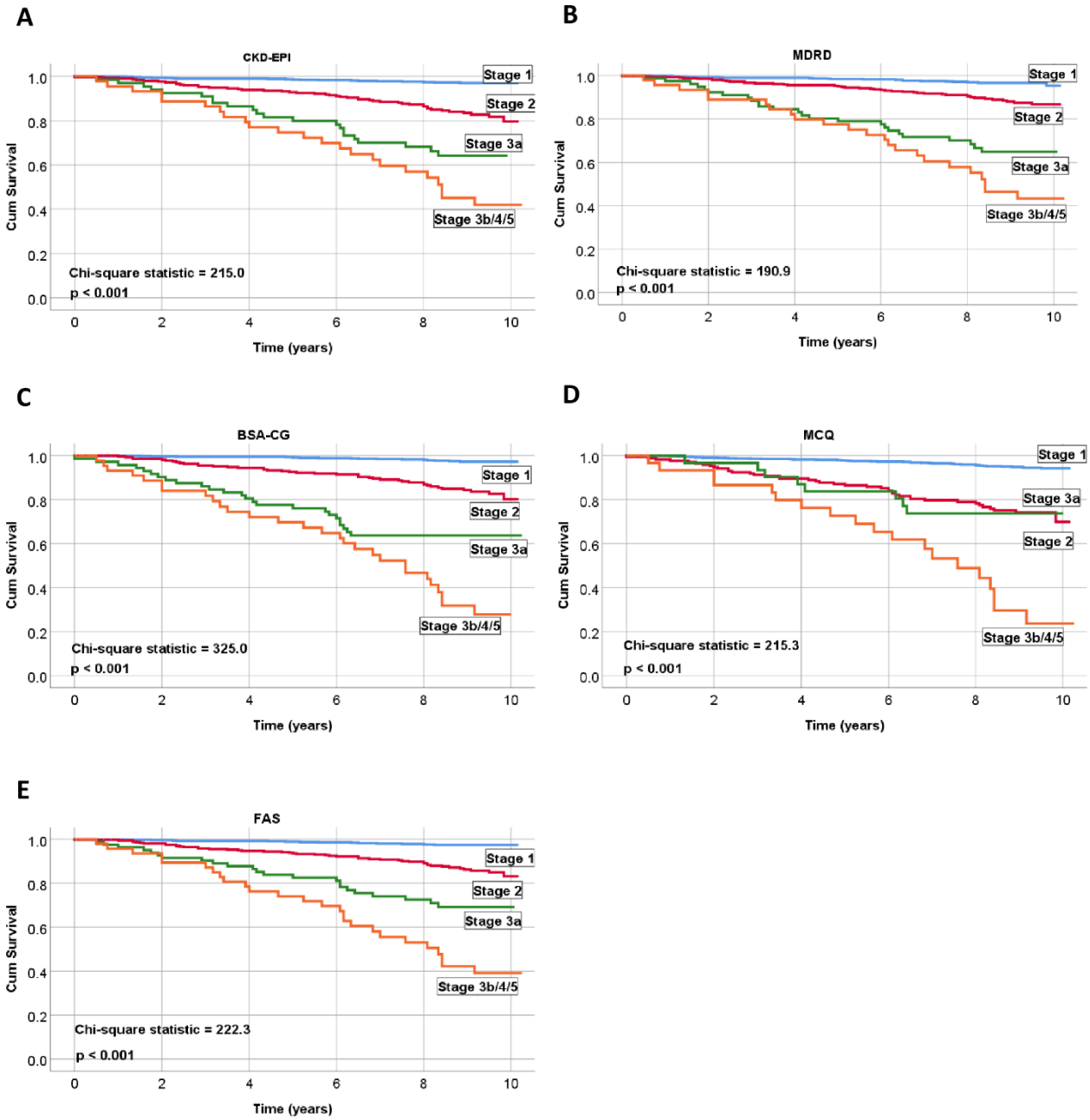


Fig 1. Unadjusted Kaplan-Meier survival curves for all-cause mortality according to the different eGFR and CrCl equations. CG: body surface area-adjusted Cockcroft-Gault; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration; CrCl: creatinine clearance; FAS: Full Age Spectrum; MCQ: Mayo Clinic Quadratic; MDRD: Modification of Diet in Renal Disease Study.

Table 2. Hazard ratios for the association of eGFR and CrCl with all-cause mortality.

eGFR and CrCl equations	Unadjusted HR (95% CI)	*P*-value	Adjusted[a] HR (95% CI)	*P*-value
CKD-EPI				
Stage 1	Reference		Reference	
Stage 2	6.25 (3.70–10.55)	<0.001	2.44 (1.31–4.55)	0.005
Stage 3a	15.02 (8.20–27.54)	<0.001	5.93 (2.92–12.03)	<0.001
Stage 3b/4/5	25.41 (13.94–46.29)	<0.001	7.31 (3.56–15.03)	<0.001
MDRD				
Stage 1	Reference		Reference	
Stage 2	3.52 (2.09–5.92)	<0.001	2.03 (1.17–3.54)	0.012
Stage 3a	12.10 (6.77–21.62)	<0.001	5.55 (2.95–10.44)	<0.001
Stage 3b/4/5	19.92 (11.02–36.01)	<0.001	5.98 (3.10–11.54)	<0.001
BSA-CG				
Stage 1	Reference		Reference	
Stage 2	7.08 (4.03–12.44)	<0.001	3.16 (1.49–6.72)	0.003
Stage 3a	19.79 (10.68–36.67)	<0.001	8.18 (3.63–18.44)	<0.001
Stage 3b/4/5	42.02 (22.96–76.88)	<0.001	13.49 (5.75–31.66)	<0.001
MCQ				
Stage 1	Reference		Reference	
Stage 2	5.75 (3.76–8.80)	<0.001	3.04 (1.84–5.02)	<0.001
Stage 3a	5.81 (2.73–12.35)	<0.001	2.45 (1.11–5.40)	0.026
Stage 3b/4/5	19.40 (11.28–33.36)	<0.001	6.23 (3.41–11.37)	<0.001
FAS				
Stage 1	Reference		Reference	
Stage 2	5.91 (3.31–10.55)	<0.001	2.42 (1.17–4.97)	0.017
Stage 3a	14.83 (7.74–28.43)	<0.001	4.94 (2.20–11.11)	<0.001
Stage 3b/4/5	32.11 (17.00–60.68)	<0.001	8.15 (3.61–18.41)	<0.001

BSA-CG: body surface area-adjusted Cockcroft-Gault; CI: confidence interval; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CVD: cardiovascular disease; DM: diabetes mellitus; FAS: Full Age Spectrum; HR: hazard ratio; HTN: hypertension; MCQ: Mayo Clinic Quadratic; MDRD: Modification of Diet in Renal Disease Study.

[a]Multivariable Cox model adjusted for age (categories), sex, CVD, DM, HTN, history of smoking, dyslipidemia, obesity, and cancer.

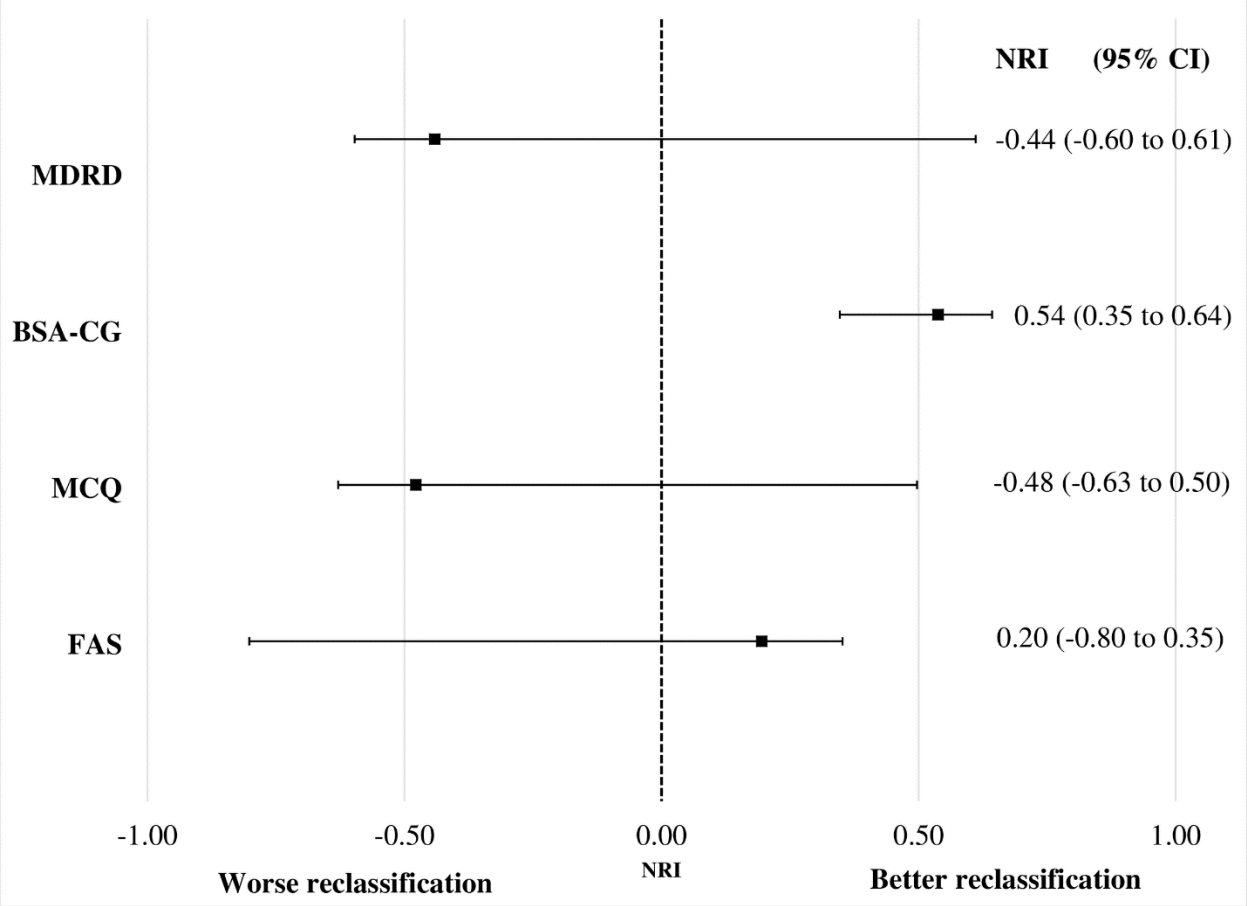


Fig 2. NRI of different eGFR and CrCl equations compared with CKD-EPI formula using CKD stages after multivariable adjustment[a]. BSA-CG: body surface area-adjusted Cockcroft-Gault; CKD: chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CrCl: creatinine clearance;
eGFR: estimated glomerular filtration; FAS: Full Age Spectrum; MCQ: Mayo Clinic Quadratic; MDRD: Modification of Diet in Renal Disease Study; NRI: Net Reclassification Indices.
[a]Multivariable Cox model adjusted for age (categories), sex, CVD, DM, HTN, history of smoking, dyslipidemia, obesity, and cancer.

Results of the analysis on the discriminative abilities for predicting all-cause mortality among high-risk UAE nationals are shown in Table 3. In the unadjusted models, when compared with the CKD-EPI equation (*C*-index: 0.779), MDRD and FAS equations did not have better discriminative abilities. The MCQ equation discriminated poorly, whereas the BSA-CG equation had the best discrimination (*C*-index: 0.816; $P = 0.004$). Even after adjustment for other confounding variables (age, sex, CVD, DM, HTN, history of smoking, dyslipidemia, obesity, and cancer), the BSA-CG equation was the most accurate in predicting all-cause mortality. In addition, this study demonstrated a significant increase in the NRI and IDI with the BSA-CG equation, when compared with the CKD-EPI equation after multivariable adjustment, while no significant differences were observed among the MDRD, MCQ, and FAS equations for predicting all-cause mortality (Table 4 and Fig 2).

Table 3. Discriminative abilities of eGFR and CrCl equations for predicting all-cause mortality.

eGFR and CrCl equations	**Unadjusted**			**Adjusted[a]**		
	***C*-indices ± SD**	**Difference of *C*-indices**	***P*-value**	***C*-indices ± SD**	**Difference of *C*-indices**	***P*-value**
CKD-EPI	0.779 ± 0.022	Reference		0.861 ± 0.016	Reference	
MDRD	0.753 ± 0.023	-0.026	0.059	0.863 ± 0.015	0.002	0.567
BSA-CG	0.816 ± 0.020	0.037	0.004	0.869 ± 0.016	0.008	0.037
MCQ	0.728 ± 0.024	-0.051	0.003	0.856 ± 0.017	-0.005	0.184
FAS	0.781 ± 0.021	0.002	0.887	0.859 ± 0.016	-0.002	0.516

BSA-CG: body surface area-adjusted Cockcroft-Gault; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CVD: cardiovascular disease; DM: diabetes mellitus; FAS: Full Age Spectrum; HTN: hypertension; IDI: Integrated Discrimination Increment; MCQ: Mayo Clinic Quadratic; MDRD: Modification of Diet in Renal Disease Study; NRI: Net Reclassification Indices; SD: standard deviation; eGFR: estimated glomerular filtration; CrCl: creatinine clearance.

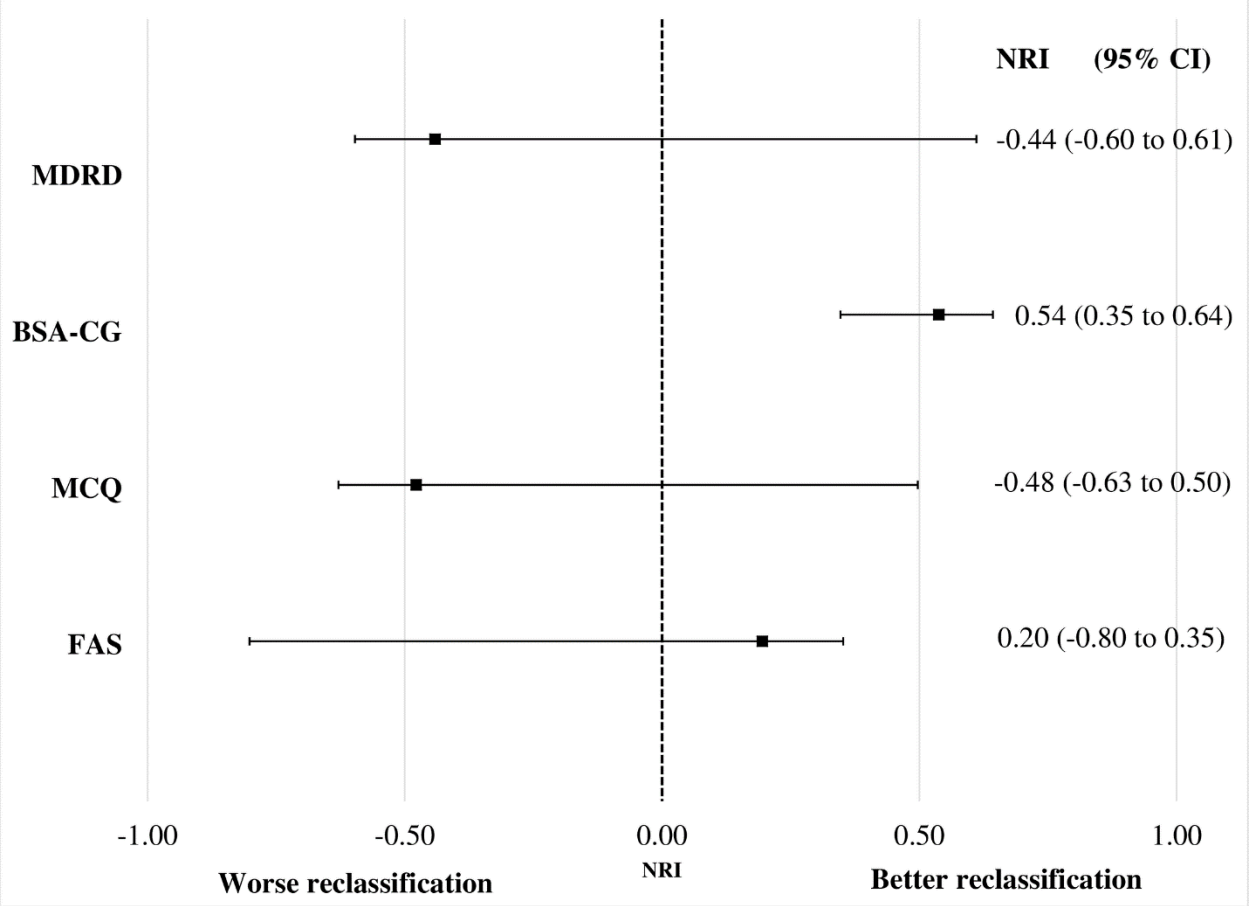
[a]Multivariable Cox model adjusted for age (categories), sex, CVD, DM, HTN, history of smoking, dyslipidemia, obesity, and cancer.

Table 4. Reclassification performance of eGFR and CrCl equations for predicting all-cause mortality, based on IDI after multivariable adjustment[a].

eGFR and CrCl equations	**IDI, (95% CI)**	***P*-value**
CKD-EPI	Reference	
MDRD	-0.014 (-0.060–0.020)	0.416
BSA-CG	0.087 (0.029–0.147)	0.008
MCQ	-0.029 (-0.079–0.014)	0.172
FAS	-0.003 (-0.038–0.036)	0.871

BSA-CG: body surface area-adjusted Cockcroft-Gault; CI: confidence interval; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CrCl: creatinine clearance. eGFR: estimated glomerular filtration; FAS: Full Age Spectrum; IDI: Integrated Discrimination Increment; MCQ: Mayo Clinic Quadratic; MDRD: Modification of Diet in Renal Disease Study.

[a]Multivariable Cox model adjusted for age (categories), sex, CVD, DM, HTN, history of smoking, dyslipidemia, obesity, and cancer.



DISCUSSION

Our study results showed that the BSA-CG formula performed slightly better than the CKD-EPI equation with respect to both discriminative ability as well as reclassification for predicting all-cause mortality in this high-risk Emirati population. It must be emphasized that our study's aim was not to accurately determine renal function in order to classify kidney failure, but rather to assess the prognostic value of different renal function formulas on all-cause mortality in our cohort of patients with vascular risk.

Predicting prognosis using renal function has been extensively studied in different populations [24–29], but the formula of choice for mortality prediction has yet to be definitively established.

Studies have shown that the CKD-EPI formula outperforms the CG and MDRD equations in accuracy and precision when estimating GFR [10,14] particularly in population-based studies. Therefore, it would logically follow that calculating the renal function using the CKD-EPI equation would also prognosticate and predict mortality more accurately than other formulas. Surprisingly, when we compared the discriminative abilities for predicting all-cause mortality among high-risk UAE nationals, the BSA-CG formula had significantly better discrimination than the CKD-EPI formula (C-indices: 0.869 vs. 0.861, $P = 0.037$, respectively). Moreover, compared to the CKD-EPI equation, the NRI value of the BSA-CG formula was significantly positive for all-cause mortality. Interestingly, similar results were also seen in previous studies assessing predictive outcomes in patients with vascular risk [26,28,29,38]. In the Heart Omics in Ageing (HOMAGE) study, the BSA-CG equation was found to be slightly more accurate in predicting cardiovascular disease mortality in patients with CVD risk [26]. In addition, a large Swedish cohort study in patients with heart failure found that the CG (BSA unadjusted) equation predicted mortality most accurately when compared with the CKD-EPI and MDRD equations [28]. Similar results were noted in a recent study on patients with acute coronary syndrome, in which the BSA-CG and FAS equations were superior in predicting one-year mortality compared to the CKD-EPI equation [29].

Our study results may be explained by the difficulty for a direct comparison between the CKD-EPI and CG formulas, e.g., the CKD-EPI equation measures the relative renal function, while the CG formula measures the absolute renal function. In addition, unlike the CKD-EPI formula, the CG equation includes the anthropometric measurement of weight in the calculation. It has been shown that obesity increases the risk of developing diabetes and HTN [39], and close to half and two-thirds of our study population had these comorbidities, respectively. Collectively

these vascular risk factors have a direct effect, by increasing the risk for kidney disease [40] as well as all-cause mortality in these patients [41]. Furthermore, the CG equation has been shown to be a better predictor of renal function in overweight and obese patients with vascular comorbidities than the CKD-EPI formula [42]. With close to half of our study participants being obese at baseline, could possibly explain why the BSA-CG equation is a relatively better predictor of mortality in our population than the CKD-EPI formula. Moreover, despite adjusting for obesity, the BSA-CG equation remained the best predictor of all-cause mortality.

The findings from this and recent large cohort studies suggest that the BSA-CG equation has the potential to improve long-term prediction of mortality in high-risk patients compared to the currently recommended CKD-EPI formula [26,28,29]. Therefore, the BSA-CG equation may have some clinical and research implications as a prognostic indicator in this high-risk population.

Strengths and Limitations

To the best of our knowledge, this is the first study that compares the prognostic abilities of different creatinine-based eGFR and CrCl equations in Emirati patients with vascular risk over a 9-year period. In addition, this study used recorded anthropometric and laboratory data rather than self-reported measurements for the classification of risk factors.

This study has several limitations. First, our study's purpose was to assess eGFR and CrCl equations with respect to the prediction of all-cause mortality and not to identify which formula most accurately predicts true GFR. Thus, the method to best measure true GFR cannot be determined from our study. Second, data on other prognostic CKD markers for mortality, such as albuminuria or cystatin-C, were unavailable and could have affected the study results. Finally,

changes in creatinine levels from baseline were not accounted for during the follow-up period, which could have affected the predictive abilities of the different eGFR and CrCl equations.

CONCLUSIONS

Knowing the formula that performs best prognostically in our at-risk population may help to better define those at the highest risk and decide on the most appropriate treatment plans and interventions. The results of our study suggest that the BSA-CG equation may have the potential to slightly improve mortality prediction in Emirati patients with vascular risk and could potentially have a prognostic role in these patients in everyday clinical practice or research. However, further large multicenter studies from the region are warranted to confirm our findings.

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Not applicable.

Author contributions

S.A.S. contributed to the research idea and design of the study. S.A.S. contributed to acquisition of data. S.A.S., R.D.G., J.K. contributed to the interpretation of data, and S.A.S. was responsible for the statistical analysis. S.A.S. drafted the manuscript. S.A.S., R.D.G., J.K. contributed to the critical revision of the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

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Conflict of interest statement

None of the authors have any financial conflict of interest with the information presented in this article. The results presented in this article have not been published previously in whole or in part.

Data availability statement

Data are available in a public, open-access repository. Supplementary data and analysis can be accessed from the Mendeley repository (http://dx.doi.org/10.17632/ppfwfpprbc.1). All data have been provided in the study and anyone is permitted to use the data provided that the article is properly cited.

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