Original Article

KIDNEY RESEARCH
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Comparison of cardiovascular event predictability between the 2009 and 2021 Chronic Kidney Disease Epidemiology Collaboration equations in a Korean chronic kidney disease cohort: the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease study

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Background: The 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine-based estimated glomerular filtration rate (eGFRcr) equation contains a race component that is not based on biology and may cause a bias in results. Therefore, the 2021 eGFRcr and creatinine-cystatin C–based eGFR (eGFRcr-cysC) equations were developed with no consideration of race. This study compared the cardiovascular event (CVE) and all-cause mortality and CVE combined predictability among the three eGFR equations in Korean chronic kidney disease (CKD) patients.
Methods: This study included 2,207 patients from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease. Receiver operating characteristic (ROC) and net reclassification improvement (NRI) index were used to compare the predictability of the study outcomes according to the 2009 eGFRcr, 2021 eGFRcr, and 2021 eGFRcr-cysC equations.
Results: The overall prevalence of CVE and all-cause mortality were 9% and 7%, respectively. There was no difference in area under the curve of ROC for CVE and mortality and CVE combined among all three equations. Compared to the 2009 eGFRcr, both the 2021 eGFRcr (NRI, 0.013; 95% confidence interval [CI], – 0.002 to 0.028) and the eGFRcr-cysC (NRI, –0.001; 95% CI, –0.031 to 0.029) equations did not show improved CVE predictability. Similar findings were observed for mortality and CVE combined predictability with both the 2021 eGFRcr (NRI, –0.019; 95% CI, –0.039–0.000) and the eGFRcr-cysC (NRI, –0.002; 95% CI, –0.023 to 0.018).
Conclusion: The 2009 eGFRcr equation was not inferior to either the 2021 eGFRcr or eGFRcr-cysC equation in predicting CVE and the composite of mortality and CVE in Korean CKD patients.

Keywords: Cardiovascular diseases, Chronic renal insufficiency, Creatinine, Cystatin C, Racial groups

Introduction

Estimated glomerular filtration rate (eGFR) is a surrogate marker of kidney function calculated using endogenous filtration byproducts of creatinine and cystatin C (cysC). In 1999, the Modification of Diet in Renal Disease (MDRD) eGFR equation was developed from a cohort of Caucasian and African-American chronic kidney disease (CKD) patients with glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 [1]. However, eGFR calculated from this equation was often underestimated in patients with GFR greater than 60 mL/min/1.73 m^2. To overcome this limitation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) developed a new eGFR equation using creatinine in 2009. The new equation was more accurate than that of the MDRD, especially in patients with GFR less than 60 mL/min/1.73 m^2 [2]. Since the introduction of the 2009 CKD-EPI eGFR creatinine (eGFRcr) equation, it has been employed widely in global medical practice.

Factors including ethnicity, age, and sex, which are associated with amount of muscle mass and muscle metabolism, affect the creatinine level and, consequently, eGFR calculations [3]. Young to middle-aged African-Americans, especially males, often have higher creatinine levels compared to Caucasians [4]. Therefore, both MDRD and CKD-EPI eGFRcr equations had correction factors for age, sex, and African-American race [1,2]. However, this led to disproportionate diagnosis of CKD in different ethnicities due to varying levels of creatinine and cysC and use of a 'race' coefficient developed to correct eGFR difference between African-American and white individuals [5]. Also, lack of consideration of individual diversity in African-Americans often led to inappropriate early or delayed referral to nephrologists [6,7]. Therefore, in 2021, the CKD-EPI group developed two new eGFR equations using creatinine (eGFRcr) and creatinine-cysC (eGFRcr-cysC) and omitting the race factor [8].

In 2022, the National Kidney Foundation and American Society of Nephrology published a joint statement that recommends use of the 2021 eGFRcr or eGFRcr-cysC equation over the current 2009 eGFRcr equation [9]. Other studies have also reported that the 2021 eGFR equations were more accurate than the 2009 eGFRcr equation, especially in African-Americans with lower kidney function [10,11]. Therefore, the new 2021 equations have the greatest bene-fits in CKD screening, detection, and risk prediction in African-Americans adults [9]. However, its benefits in an Asian population are unclear as the percentage of Asian CKD patients included in previous landmark studies was low, and those included were classified as 'non-black,' which mostly included Caucasians [8,10,11]. Also, previous studies that proposed an Asian coefficient for MDRD and 2009 CKD-EPI eGFR equations reported variable values depending on Asian ethnicity and study methods [12].

It is widely known that cardiovascular morbidity and mortality risk are elevated in both early and advanced stages of CKD [13,14]. Therefore, it is important to accurately predict cardiovascular event (CVE) risk in CKD patients. As Korea is a monoethnic Asian country, this study was conducted to evaluate the efficiency of the new 2021 eGFRcr and eGFRcr-cysC equations, which do not include a race factor, compared to the 2009 eGFRcr equation. The predictability of CVE and composite of all-cause mortality and CVE among eGFR equations was compared in a Korean nondialysis CKD cohort.

Methods

Study design

The KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) is a national, prospective, multicenter study of Korean nondialysis CKD patients from nine major nephrology centers of university hospitals in Korea. Study exclusion criteria are 1) inability or unwillingness to provide written consent; 2) previous maintenance dialysis or organ transplantation; 3) heart failure (New York Heart Association functional class 3 or 4) or cirrhosis (Child-Pugh class 2 or 3); 4) history of or current malignancy; 5) pregnancy; or 6) single kidney due to trauma or donation.

From September 2011 to January 2016, a total of 2,238 adult nondialysis CKD patients between the ages of 20 and 75 years were enrolled. Patients with missing information on CVE and all-cause mortality due to follow-up loss within 6 months of study entry were excluded.

The KNOW-CKD study was conducted in accordance with the principles of the Declaration of Helsinki and was supervised by the Korea Centers for Disease Control and Prevention. The study was approved by the Institutional

Review Boards of all nine university hospitals including Seoul National University Hospital in 2011 (No. 1104-089-359). A detailed study protocol of the KNOW-CKD has been previously published [15].

Laboratory and clinical variables

All laboratory and clinical variables were collected from patients on their initial visit to the enrolled hospital.

Blood samples were collected after at least 8 hours of fasting. Baseline laboratory measurements were hemoglobin (Hb), blood urea nitrogen (BUN), creatinine, cysC, sodium, potassium, calcium, phosphorus, uric acid, parathyroid hormone (PTH), high-sensitivity C-reactive protein (hs-CRP), troponin T, fasting glucose, HbA1C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Serum creatinine, cysC, PTH, and urine protein and creatinine values were measured at one central laboratory (LabGenomics). Serum creatinine was measured using the isotope dilution mass spectrometry-traceable method, and serum cysC was measured using the immunonephelometry method for consistency [16]. Other laboratory measurements were conducted in the appropriate hospital laboratory.

Baseline clinical information on age, sex, underlying comorbidity, medication, and lifestyle patterns including cigarette smoking status (never, former, current) were collected using self-reported questionnaires with the assistance of trained staff. Information regarding CVE was collected through medical interview and review of the patient's electronic medical records during the hospital visits initially and at 6 months after enrollment and annually after that. Review of the CVE by the nephrologist in charge of the KNOW-CKD study in each hospital was repeated, and CVE was classified into 10 categories: acute myocardial infarction, hospitalization for unstable angina or heart failure, percutaneous coronary artery intervention or coronary bypass graft surgery, ischemic stroke, hemorrhagic stroke, carotid artery disease, peripheral artery disease, symptomatic arrhythmia, and any other CVE that required hospitalization or intervention. Finally, CVE was cross-checked by another nephrologist among the participating hospitals of the KNOW-CKD study to ensure accuracy and objectivity of the outcome data. For fatal CVE, information regarding the time and causes of mortality was obtained from the patient's electronic medical records or the Korean Statistical Information Service.

Blood pressure was measured by a trained nurse using an electronic sphygmomanometer after 5 minutes of rest in a sitting position. Hypertension was defined as (a) systolic blood pressure (SBP) of >140 mmHg or diastolic blood pressure (DBP) of >90 mmHg or (b) previous diagnosis of hypertension. Mean arterial pressure (MAP) was calculated using the following equation: MAP = DBP + 1/3 (SBP – DBP).

Diabetes mellitus (DM) was defined as (a) fasting serum glucose of >126 mg/dL or (b) previous diagnosis of DM.

Estimated glomerular filtration rate calculation

Each eGFR was calculated using three CKD-EPI equations: 2009 CKD-EPI eGFRcr, 2021 CKD-EPI eGFRcr, and 2021 eGFRcr-cysC equations [2,8]. These equations are listed below.

2009 CKD-EPI eGFRcr equation
Female
- Serum creatinine (Scr) ≤ 0.7 mg/dL: $144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
- Scr > 0.7 mg/dL: $144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$

Male
- Scr ≤ 0.9 mg/dL: $141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
- Scr > 0.9 mg/dL: $141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

2021 CKD-EPI eGFRcr equation
Female
- Scr ≤ 0.7 mg/dL: $142 \times (Scr/0.7)^{-0.241} \times 0.9938^{Age} \times 1.012$
- Scr > 0.7 mg/dL: $142 \times (Scr/0.7)^{-1.200} \times 0.9938^{Age} \times 1.012$

Male
- Scr ≤ 0.9 mg/dL: $142 \times (Scr/0.9)^{-0.302} \times 0.9938^{Age}$
- Scr > 0.9 mg/dL: $142 \times (Scr/0.9)^{-1.200} \times 0.9938^{Age}$

2021 CKD-EPI eGFRcr-cysC equation
Female
- Scr ≤ 0.7 mg/dL
1) Serum cysC (ScysC) ≤ 0.8 mg/dL:
   $135 \times (Scr/0.7)^{-0.219} \times (ScysC/0.8)^{-0.323} \times 0.9961^{Age} \times 0.963$

2) ScysC > 0.8 mg/dL:

$135 \times (\text{Scr}/0.7)^{-0.219} \times (\text{ScysC}/0.8)^{-0.778} \times 0.9961^{\text{Age}} \times 0.963$

- Scr > 0.7 mg/dL

1) ScysC ≤ 0.8 mg/dL:

$135 \times (\text{Scr}/0.7)^{-0.544} \times (\text{ScysC}/0.8)^{-0.323} \times 0.9961^{\text{Age}} \times 0.963$

2) ScysC > 0.8 mg/dL:

$135 \times (\text{Scr}/0.7)^{-0.544} \times (\text{ScysC}/0.8)^{-0.778} \times 0.9961^{\text{Age}} \times 0.963$

Male

- Scr ≤ 0.9 mg/dL

1) ScysC ≤ 0.8 mg/dL:

$135 \times (\text{Scr}/0.9)^{-0.144} \times (\text{ScysC}/0.8)^{-0.323} \times 0.9961^{\text{Age}}$

2) ScysC > 0.8 mg/dL:

$135 \times (\text{Scr}/0.9)^{-0.144} \times (\text{ScysC}/0.8)^{-0.778} \times 0.9961^{\text{Age}}$

- Scr > 0.9 mg/dL

1) ScysC ≤ 0.8 mg/dL:

$135 \times (\text{Scr}/0.9)^{-0.544} \times (\text{ScysC}/0.8)^{-0.323} \times 0.9961^{\text{Age}}$

2) ScysC > 0.8 mg/dL:

$135 \times (\text{Scr}/0.9)^{-0.544} \times (\text{ScysC}/0.8)^{-0.778} \times 0.9961^{\text{Age}}$

Study outcomes

As cardiovascular disease is one of the most critical complications of CKD, primary outcome was defined as the first occurrence of either non-fatal or fatal CVE. CVE included acute myocardial infarction, hospitalization for unstable angina or heart failure, percutaneous coronary artery intervention or coronary bypass graft surgery, ischemic stroke, hemorrhagic stroke, carotid artery disease, peripheral artery disease, symptomatic arrhythmia, or any other CVE that required hospitalization or intervention. The secondary outcome was the composite event of all-cause mortality and CVE.

Statistical analysis

Baseline characteristics were analyzed according to CVE. Continuous variables were expressed as mean ± standard deviation or median and interquartile range and analyzed using the Kruskal-Wallis test or one-way analysis of variance. Categorical variables were expressed as percentages. Comparison of categorical variables was conducted using chi-square test. Cox proportional hazard analysis was used to evaluate the predictive risk of CVE and all-cause mortality and CVE combined according to eGFR equation.

Evaluated risks were expressed as hazard ratio (HR) and 95% confidence interval (CI). For Cox proportional hazard analysis, the multivariable model was adjusted for age, sex, DM, smoking, body mass index (BMI), MAP, LDL-C, ejection fraction (EF), and proteinuria (urine protein/creatinine ratio, >0.2 g/day). Receiver operating characteristic (ROC) curve analysis was conducted to compare the predictability of the three equations on study outcome. Also, the nenet reclassification improvement (NRI) index was calculated to compare improvement in predictability of one equation over another. The multivariable model for ROC and NRI analysis was adjusted for age, sex, DM, smoking, BMI, MAP, LDL-C, and EF. Two-sided p-values of <0.05 were considered statistically significant. All statistical analyses were performed using R version 4.0.4 (R Foundation for Statistical Computing).

Results

Baseline characteristics of the study population

From September 2011 to January 2016, a total of 2,238 adult nondialysis CKD patients between the ages of 20 and 75 years were enrolled. Among them, 31 patients were excluded due to missing information on CVE and all-cause mortality or to follow-up loss within 6 months of study entry. Finally, 2,207 patients were enrolled in this study. The median follow-up duration of the above patients was 8.6 years (Fig. 1).

Among the total of 2,207 patients, the overall prevalence of CVE was 9.1% (n = 200). The types of CVE experienced
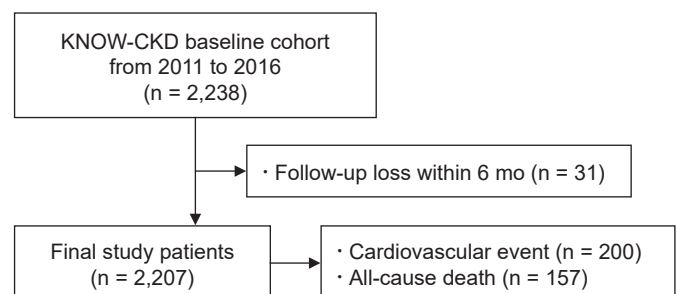
Figure 1. Flow diagram of patient enrollment.
KNOW-CKD, KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease.

by the 200 patients included acute myocardial infarction (n = 24), hospitalization for unstable angina (n = 23), hospitalization for heart failure (n = 14), percutaneous coronary artery intervention or coronary bypass graft surgery (n = 25), ischemic stroke (n = 34), hemorrhagic stroke (n = 17), carotid artery disease (n = 2), peripheral artery disease (n = 7), symptomatic arrhythmia (n = 13), and any other CVE that required hospitalization or intervention (n = 41).

Baseline characteristics of the study population were compared according to the presence of CVE. CVE patients were older with a larger percentage of males. In CVE patients, serum BUN, creatinine, and cysC levels were slightly higher and the eGFR level calculated using the 2009 eGFRcr equation was slightly lower than in non-CVE patients. Also, fasting glucose and HbA1C levels were higher with a higher percentage of underlying DM. Regarding the cardiovascular aspect, the percentage of patients with underlying coronary artery disease was approximately six-fold higher (23.5% vs. 4.3%, p < 0.001) in patients with CVE. In addition, CVE patients had slightly higher levels of hs-CRP and troponin T and lower left ventricular EF percentage as measured with echocardiogram. In comparison of lipid profiles, CVE patients had lower HDL-C, LDL-C, and total cholesterol levels. Regarding lifestyle, the percentages of current and former smokers were higher among CVE patients (Table 1).

Comparison of estimated glomerular filtration rate level according to estimated glomerular filtration rate equation

In comparison of the three eGFR equations, eGFR level was approximately 3 mL/min/1.73 m^2 higher when calculated using the 2021 eGFRcr equation and 1.5 mL/min/1.73 m^2 higher when calculated using the 2021 eGFRcr-cysC equation compared to that calculated using the 2009 eGFRcr equation. The distribution of difference in calculated eGFR level between eGFR equations is shown using the Bland-Altman plot (Fig. 2).

In comparison of 2009 and 2021 eGFRcr equations, CKD stage classification according to the 2021 eGFRcr equation allocated a higher number of patients to CKD stages 1 and 2 (38.9% vs. 35.1%) and a lower number of patients to CKD stages 3 to 5 (61.1% vs. 64.9%). A similar trend was observed when CKD stages were classified according to the 2021 eGFRcr-cysC equation. Prevalence of CVE and composite of all-cause mortality and CVE were highest in patients with CKD stages 3 and 4 for all three equations (Table 2).

Predictive value of estimated glomerular filtration rate for cardiovascular event and composite of all-cause mortality and cardiovascular event

The predictive value of eGFR for CVE, calculated using each of the three eGFR equations, was statistically significant only in the unadjusted model. In that model, every 10 mL/min/1.73 m^2 increase in eGFR was associated with lower predicted risk of CVE in all three equations (2009 eGFRcr equation: HR, 0.90; 95% CI, 0.86–0.95; 2021 eGFRcr equation: HR, 0.91; 95% CI, 0.87–0.96; and 2021 eGFRcr-cysC equation: HR, 0.90; 95% CI, 0.85–0.95). However, in prediction of the composite of all-cause mortality and CVE, significantly lower predictive risks were observed in all univariate and multivariate models across all three equations (2009 eGFRcr equation: HR, 0.94; 95% CI, 0.89–0.99; 2021 eGFRcr equation: HR, 0.94, 95% CI, 0.90–0.99; and 2021 eGFRcr-cysC equation: HR, 0.92, 95% CI, 0.87–0.97) (Table 3).

Comparison of cardiovascular event and the composite of all-cause mortality and cardiovascular event predictability

The area under the ROC curve (AUC) for CVE predictability was similar among the three equations (2009 eGFRcr equation: 0.715; 95% CI, 0.679–0.752; 2021 eGFRcr equation: 0.715; 95% CI, 0.679–0.752; and 2021 eGFRcr-cysC equation: 0.716; 95% CI, 0.679–0.753) (Fig. 3A). Similar findings were observed in comparison of predictability for the composite of all-cause mortality and CVE with slightly increased AUC value for the 2021 eGFRcr-cysC equation compared to that of 2009 and 2021 eGFRcr equations (2009 eGFRcr equation: 0.747; 95% CI, 0.719–0.776; 2021 eGFRcr equation: 0.747; 95% CI, 0.719–0.776; and 2021 eGFRcr-cysC equation: 0.751; 95% CI, 0.723–0.779) (Fig. 3B).

Additionally, NRI was used to compare the predictability of CVE and the composite of all-cause mortality and CVE among eGFR equations. Neither the 2021 eGFRcr nor 2021 eGFRcr-cysC equation had improved predictive power for CVE and all-cause mortality outcomes compared to the 2009 eGFRcr equation, and none of the NRI values were

Table 1. Baseline characteristics of study population according to CVE

Characteristic	Total	CVE (+) group	CVE (−) group	p-value
No. of patients	2,207	200	2,007	
Age (yr)	55.0 (45.0–63.0)	61.0 (55.0–67.5)	54.0 (44.0–63.0)	<0.001
Male sex	1,353 (61.3)	145 (72.5)	1,208 (60.2)	0.001
BMI (kg/m^2)	24.4 (22.3–26.5)	24.4 (22.6–26.0)	24.4 (22.3–26.5)	0.65
Hb (g/dL)	12.8 (11.3–14.3)	12.5 (10.8–14.1)	12.8 (11.3–14.4)	0.09
BUN (mg/dL)	24.0 (17.0–35.0)	27.6 (19.9–35.5)	23.6 (17.0–35.0)	0.01
Creatinine (mg/dL)	1.5 (1.1–2.2)	1.7 (1.2–2.3)	1.5 (1.0–2.2)	0.02
Cystatin C (mg/dL)	1.5 (1.1–2.2)	1.7 (1.3–2.2)	1.5 (1.0–2.2)	0.003
eGFR[a] (mL/min/1.73 m^2)	46.2 (28.3–73.0)	41.8 (28.2–60.3)	47.4 (28.4–75.0)	0.006
Sodium (mEq/L)	143.0 (140.0–148.0)	142.0 (139.0–148.0)	143.0 (140.0–148.0)	0.046
Potassium (mEq/L)	6.1 (5.1–9.0)	6.2 (5.3–8.6)	6.1 (5.1–9.0)	0.95
Calcium (mg/dL)	9.4 (9.1–9.8)	9.3 (9.0–9.6)	9.5 (9.1–9.8)	0.004
Phosphorus (mg/dL)	5.0 (4.2–6.3)	4.9 (4.1–6.2)	5.1 (4.2–6.3)	0.29
Uric acid (mg/dL)	7.0 (5.8–8.3)	7.2 (5.9–8.5)	7.0 (5.8–8.3)	0.73
PTH (pg/dL)	51.0 (34.8–79.8)	49.4 (33.2–76.4)	51.1 (35.0–79.9)	0.64
hs-CRP (mg/dL)	0.6 (0.2–1.7)	0.8 (0.3–1.8)	0.6 (0.2–1.7)	0.03
Troponin T (ng/mL)	0.01 (0.01–0.02)	0.02 (0.01–0.03)	0.01 (0.01–0.02)	<0.001
Fasting glucose (mg/dL)	100.0 (92.0–114.5)	107.0 (93.0–129.5)	99.0 (92.0–113.0)	0.001
HbA1C (%)	6.4 (5.7–7.5)	6.9 (6.1–7.8)	6.4 (5.7–7.3)	<0.001
Total cholesterol (mg/dL)	171.0 (146.0–198.0)	161.0 (135.0–191.0)	171.0 (147.0–199.0)	0.002
HDL-C (mg/dL)	47.0 (38.0–58.0)	44.0 (36.0–52.5)	47.0 (38.0–58.0)	0.003
LDL-C (mg/dL)	93.0 (73.0–116.0)	88.0 (70.0–112.0)	94.0 (74.0–116.0)	0.02
Systolic BP (mmHg)	127.0 (118.0–137.0)	128.0 (116.0–139.0)	127.0 (118.0–136.0)	0.34
Diastolic BP (mmHg)	77.0 (70.0–84.0)	76.0 (69.0–82.0)	77.0 (70.0–84.0)	0.03
MAP (mmHg)	93.0 (86.0–101.0)	93.0 (85.0–100.0)	93.0 (87.0–101.0)	0.32
Ejection fraction (%)	64.0 (60.0–68.0)	63.0 (58.9–67.0)	64.0 (60.1–68.0)	0.001
Comorbidity				
Hypertension	2,114 (95.8)	197 (98.5)	1,917 (95.5)	0.07
Diabetes mellitus	741 (33.6)	105 (52.5)	636 (31.7)	<0.001
Coronary artery disease	133 (6.0)	47 (23.5)	86 (4.3)	<0.001
Smoking status[b]				0.02
Current	347 (15.8)	38 (19.1)	309 (15.4)	
Former	676 (30.7)	73 (36.7)	603 (30.1)	
Never	1,179 (53.5)	88 (44.2)	1,091 (54.5)	

Data are expressed as median (interquartile range) or number (%).
BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CVE, cardiovascular event; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; Hb, hemoglobin; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; PTH, parathyroid hormone.
[a] 2009 creatinine-based eGFR equation. [b] Patients with missing information on smoking status were excluded.

significant. Also, in comparison of the 2021 eGFRcr and eGFRcr-cysC equations, there was no difference in predictability of the study outcomes (Table 4).

Subgroup analysis of comparison of cardiovascular event and the composite of all-cause mortality and cardiovascular event predictability

As the prevalence of CVE and all-cause mortality was higher in CKD stages 3 to 5, subgroup analysis of outcome pre-
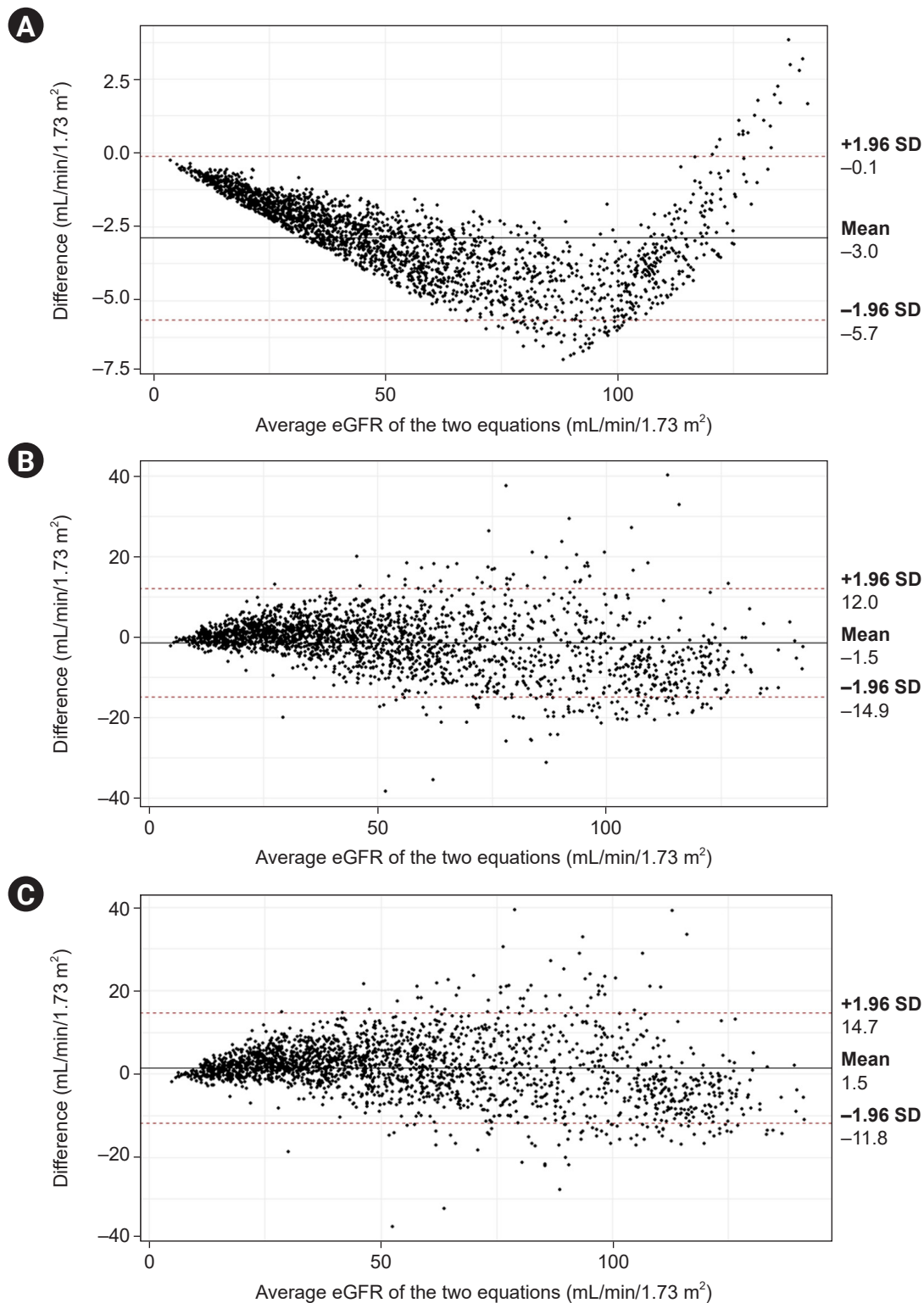
Figure 2. Bland-Altman plot of differences in eGFR among the three equations. (A) Difference between 2009 eGFRcr and 2021 eG-FRcr equation. (B) Difference between 2009 eGFRcr and 2021 eGFRcr-cysC equation. (C) Difference in eGFR between 2021 eGFRcr and 2021 eGFRcr-cysC equation.
eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcr-cysC, creatinine-cystatin C–based eGFR; SD, standard deviation.

Table 2. Comparison of average eGFR, CVE and composite of all-cause mortality and CVE prevalence according to CKD stages in each eGFR equation

Variable	2009 eGFRcr equation							2021 eGFRcr equation							2021 eGFRcr-cysC equation						
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Total	p-value	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Total	p-value	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Total	p-value
No. of patients	355	420	827	469	136	2,207		397	462	819	415	114	2,207		397	462	819	415	114	2,207	
eGFR (mL/min/1.73 m^2)	107.0 ±11.0	73.1 ±8.6	43.9 ±8.7	22.8 ±4.4	11.6 ±2.4	53.1 ±30.7	<0.001	108.7 ±10.5	73.1 ±8.8	43.8 ±8.7	22.8 ±4.3	11.9 ±2.4	56.0 ±31.5	<0.001	108.7 ±10.5	73.1 ±8.8	43.8 ±8.7	22.8 ±4.3	11.9 ±2.4	56.0 ±31.5	<0.001
CVE	12 (3.4)	39 (9.3)	88 (10.6)	53 (11.3)	8 (5.9)	200 (9.1)	<0.001	12 (3.0)	46 (10.0)	96 (11.7)	38 (9.2)	8 (7.0)	200 (9.1)	<0.001	12 (3.0)	46 (10.0)	96 (11.7)	38 (9.2)	8 (7.0)	200 (9.1)	<0.001
All-cause mortality and CVE	14 (3.9)	50 (11.9)	124 (15.0)	100 (21.3)	26 (19.1)	314 (14.2)	<0.001	15 (3.8)	61 (13.2)	133 (16.2)	82 (19.8)	23 (20.2)	314 (14.2)	<0.001	15 (3.8)	61 (13.2)	133 (16.2)	82 (19.8)	23 (20.2)	314 (14.2)	<0.001

Data are expressed as number only, mean ± standard deviation, or number (%).

CKD, chronic kidney disease; CVE, cardiovascular event; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcr-cysC, creatinine-cystatin C–based eGFR.

dictability was conducted in CKD stages 1 and 2 (eGFR of ≥60 mL/min/1.73 m^2) and 3 to 5 (eGFR of <60 mL/min/1.73 m^2) groups. In comparison of CVE prediction, AUC values were similar among all three equations in both subgroups (Supplementary Fig. 1A, B; available online). According to the NRI analysis, there was no significant improvement in predictability among the three equations in CKD stages 3 to 5. However, in CKD stages 1 and 2, the 2009 eGFRcr equation had slightly improved predictability compared to the 2021 eGFRcr equation (NRI [%], –0.048; 95% CI, –0.064 to –0.032; p < 0.001). However, no significant improvement was observed in comparison to other equations (Supplementary Table 1, available online).

In comparison of predictability of combined all-cause mortality and CVE, the AUC values were similar among the three equations in both subgroups (Supplementary Fig. 1C, D, available online). In NRI analysis, there was no significant improvement of predictability in one equation over the other in CKD stages 1 and 2. However, in CKD stages 3 to 5, the 2009 eGFRcr equation had slightly improved predictability compared to the 2021 eGFRcr equation (NRI [%], –0.026; 95% CI, – 0.050 to –0.002; p = 0.04). Also, the 2021 eGFRcr-cysC equation had slightly improved predictability compared to the 2021 eGFRcr equation (NRI [%], 0.039; 95% CI, 0.008–0.070; p = 0.01) (Supplementary Table 1, available online).

Discussion

The results of this study show that the average eGFR level calculated using the 2021 eGFRcr equation was approximately 3 mL/min/1.73 m^2 higher and 1.5 mL/min/1.73 m^2 higher than the results using the 2021 eGFRcr-cysC equation and the 2009 eGFRcr equation, respectively. There was an overall reduction in prevalence of CKD stages 3 to 5 when the 2021 eGFR equations were used for CKD stage classification (2009 eGFRcr, 64.9% vs. 2021 eGFRcr, 61.1% vs. 2021 eGFRcr-cysC, 63.4%). The AUC values for predictability of CVE and the composite of all-cause mortality and CVE were similar across equations, and the NRI values were not statistically significant. This suggests that the 2009 eGFRcr equation is not inferior in predicting CVE and the composite of all-cause mortality and CVE compared to the 2021 eGFRcr and eGFRcr-cysC equations.

The overall prevalence of CVE in this study was 9.1% (n

Table 3. Predictive value of each eGFR to CVE and composite of all-cause mortality and CVE

Variable	2009 eGFRcr (+10)	p-value	2021 eGFRcr (+10)	p-value	2021 eGFRcr-cysC (+10)	p-value
CVE						
Unadjusted	0.90 (0.86–0.95)	<0.01	0.91 (0.87–0.96)	<0.01	0.90 (0.85–0.95)	<0.01
Sex-age	0.98 (0.92–1.04)	0.46	0.98 (0.93–1.04)	0.48	0.96 (0.91–1.02)	0.15
Multivariable[a]	0.99 (0.91–1.07)	0.75	0.99 (0.91–1.07)	0.73	0.97 (0.90–1.04)	0.41
All-cause mortality and CVE						
Unadjusted	0.84 (0.80–0.88)	<0.01	0.85 (0.81–0.89)	<0.01	0.84 (0.80–0.87)	<0.01
Sex-age	0.90 (0.86–0.95)	<0.01	0.91 (0.87–0.95)	<0.01	0.89 (0.85–0.94)	<0.01
Multivariable[a]	0.94 (0.89–0.99)	0.02	0.94 (0.90–0.99)	0.02	0.92 (0.87–0.97)	<0.01

Data are expressed as hazard ratio (95% confidence interval).
CVE, cardiovascular event; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcr-cysC, creatinine-cystatin C–based eGFR.
[a]Multivariable model was adjusted for age, sex, diabetes mellitus, smoking, body mass index, mean arterial pressure, low-density lipoprotein cholesterol, ejection fraction, and proteinuria.
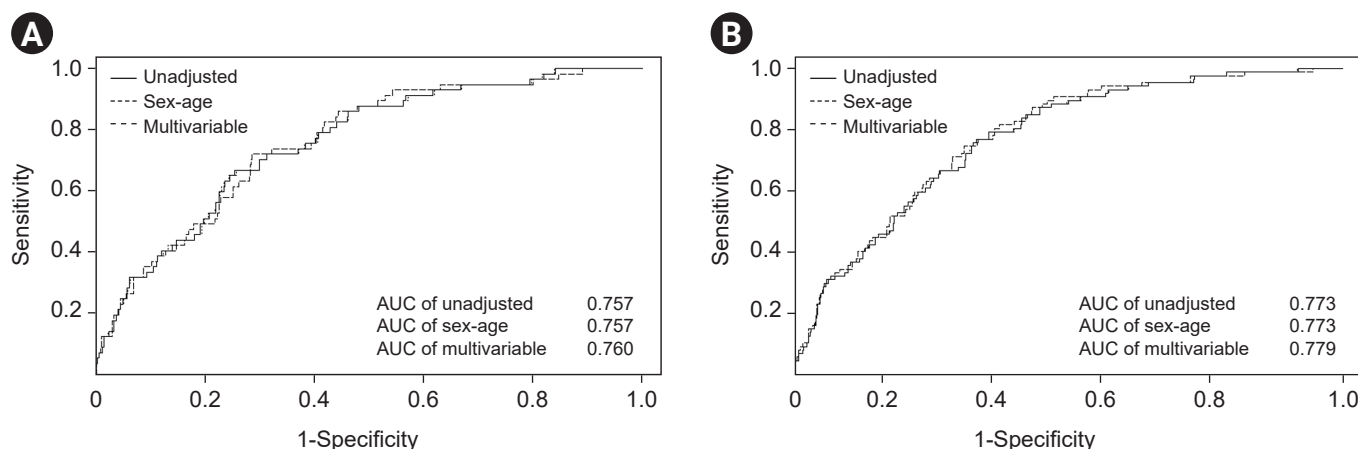
Figure 3. Receiver operating characteristic curve analysis for CVE (A) and the composite of all-cause mortality and CVE predictability (B).
AUC, area under the curve; CVE, cardiovascular event.

Table 4. NRI for comparison of predictability according to eGFR equations

Variable	NRI (%)	95% CI	p-value
CVE			
2009 eGFRcr vs. 2021 eGFRcr	0.013	–0.002 to 0.028	0.09
2009 eGFRcr vs. 2021 eGFRcr-cysC	–0.001	–0.031 to 0.029	0.94
2021 eGFRcr vs. 2021 eGFRcr-cysC	–0.015	–0.048 to 0.018	0.38
All-cause mortality and CVE			
2009 eGFRcr vs. 2021 eGFRcr	–0.019	–0.039 to 0.000	0.06
2009 eGFRcr vs. 2021 eGFRcr-cysC	–0.002	–0.023 to 0.018	0.82
2021 eGFRcr vs. 2021 eGFRcr-cysC	0.017	–0.004 to 0.039	0.11

CI, confidence interval; CVE, cardiovascular event; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcr-cysC, creatinine-cystatin C–based eGFR; NRI, net reclassification improvement.

= 200). CVE risk is increased in CKD patients and is the cause of death in approximately 40% to 50% of cases, which is approximately two-fold higher than in the general population with normal kidney function [17]. The CVE and mortality risks are increased in CKD patients through both traditional and non-traditional risk factors [13]. Traditional risk factors including DM, hypertension, dyslipidemia, and smoking aggravate atherosclerosis, which is associated not only with cardiovascular disease but also CKD progression [18]. Nontraditional risk factors include accelerated vascular calcification in vessels and cardiac valves and chronic systemic inflammation [19,20]. The overall CVE prevalence of this study was relatively low compared to other western CKD cohort studies, where the CVE prevalences were 33.4% (CRIC, United States), 47.2% (CRISIS, United Kingdom), and 39.1% (MERENA, Spain) [21–24]. Also, another study that compared longitudinal outcomes across multiple international CKD cohorts, including the current KNOW-CKD cohort, showed that the CVE risk was lower in Korean and Japanese CKD cohorts compared to western CKD cohorts [25]. This finding may be due to differences in genetics, lifestyle patterns including diet, and lower incidence of traditional cardiovascular risk factors in Asian CKD patients compared to western patients [25,26]. Due to the relatively small number of CVEs in this study, the predictive value of eGFR for CVE did not show a statistically significant association across the three eGFR equations. However, the association between eGFR and the composite of all-cause mortality and CVE was significant in both univariate and multivariate analyses, where the analysis was conducted with a larger number of clinical outcome events. This finding shows that the power of event prediction was valid and significant in all three eGFR equations. Even though the overall CVE prevalence of this study was relatively low, the CVE group had distinctive traditional and nontraditional characteristics associated with CVE. The group was older with a higher percentage of metabolic comorbidities including hypertension, DM, and coronary artery disease. Also, inflammatory markers including hs-CRP were elevated, and the percentage of former and current smokers was higher in the CVE group.

As CVE and all-cause mortality events were concentrated in CKD stage 3 to 5 patients, subgroup analysis was conducted to compare the outcome predictability in early (stages 1 and 2) and advanced (stages 3 to 5) CKD stages.

For CVE, the 2009 eGFRcr equation had slightly improved predictability compared to the 2021 eGFRcr equation in CKD stages 1 and 2. For the composite of all-cause mortality and CVE, the 2009 eGFRcr equation had slightly improved predictability compared to the 2021 eGFRcr equation. Also, the 2021 eGFRcr-cysC equation had slightly improved predictability compared to the 2021 eGFRcr equation in CKD stages 3 to 5. These findings are in line with the core results of our study that the current 2009 eGFRcr equation was not inferior to the 2021 eGFRcr and eGFRcr-cysC equations in CVE prediction. The 2021 eGFRcr-cysC equation had slightly improved predictability compared to the 2021 eGFRcr equation in advanced CKD patients, in accordance with the findings of Inker et al. [8], which showed that the 2021 eGFRcr-cysC equation was more accurate than the 2021 eGFRcr equation, with smaller differences in eGFR between the race groups. However, direct comparison of outcome predictability power and eGFR accuracy may not be appropriate.

The average eGFR level calculated using the 2021 eGFRcr equation was approximately 3 mL/min/1.73 m^2 higher and 1.5 mL/min/1.73 m^2 higher than that calculated using the 2021 eGFRcr-cysC equation and the 2009 eGFRcr equation. Therefore, approximately 10% of patients (224 of 2,207) were reclassified to a lower CKD category when using the 2021 eGFRcr equation compared to the 2009 eGFRcr equation. For the 2021 eGFRcr-cysC equation, approximately 8% of patients (181 of 2,145) were reclassified into a lower CKD category, while 7% of patients (141 of 2,147) were reclassified into a higher CKD category (Supplementary Table 2, available online). These findings are in agreement with the study by Inker et al. [8] that the calculated eGFR of the 'non-black' subpopulation was overestimated when using both 2021 eGFRcr and eGFRcr-cysC equations compared to the 2009 eGFRcr equation [8]. These findings are attributed to the changes in the variable constants of the new 2021 eGFR equations.

The prevalence of CKD 3 to 5 was reduced by 3.8% when using the 2021 eGFRcr equation and by 1.5% when using the 2021 eGFRcr-cysC equation. The Kidney Disease Improving Global Outcomes guidelines recommend thorough work-up, treatment, and regular follow-up for management of CKD and its complications, especially when the eGFR is less than 60 mL/min/1.73 m^2. CVE risk is increased dramatically in CKD stages 3 to 5, and careful examinations and

risk stratification are needed [13]. Inappropriate diagnosis of advanced CKD can be problematic in medication dose adjustment and unnecessary limitations of medication prescriptions including renin-angiotensin-system blockade agents. Even though the prevalence of CKD stages 3 to 5 was reduced using the 2021 eGFR equations, neither CVE nor the composite of all-cause mortality and CVE predictability differed with CKD 3 to 5 prevalence. This is in line with a previous study showing that the clinical significance of the new 2021 eGFR equations is minimal, especially in non-black patients [11].

The main limitation of this study is that the overall CVE prevalence was relatively low. Therefore, subtle differences in calculated eGFR among the three equations may not have sufficient statistical power to result in changes in CVE predictability. Also, there was no information on measured GFR using exogenous filtration markers. Therefore, no definite validation of accuracy of one equation over another was achieved as a direct comparison of calculated to measured eGFR values. However, to our knowledge, this is the first study to evaluate the efficacy of the 2021 eGFRcr and eGFRcr-cysC equations in a large-scale, all-Asian CKD cohort. As the KNOW-CKD study is an ongoing prospective cohort, CVE and all-cause mortality events were clearly defined and accurately documented. Also, serum creatinine and cysC were measured in a central laboratory, ensuring the accuracy of eGFR calculations.

In conclusion, the 2009 eGFRcr equation was not inferior to either the 2021 eGFRcr or eGFRcr-cysC equation in predicting risks of CVE and the composite of all-cause mortality and CVE in Korean CKD patients. Further longitudinal studies with higher CVE prevalence and availability of measured GFR are needed to validate the efficacy of the new 2021 eGFRcr and eGFRcr-cysC equations in Asian populations.

Conflicts of interest

Tae-Hyun Yoo is the Editor-in-Chief of *Kidney Research and Clinical Practice* and was not involved in the review process of this article. All authors have no other conflicts of interest to declare.

Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors' contributions

Conceptualization: JHK, MK, EK, KHO
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Formal analysis: JHK, YJ, JK
Investigation, Methodology: JK, SKP
Supervision: JCJ, THY, HL
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