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Association between Decreased Estimated Glomerular Filtration Rates and Long-term Mortality in Korean Patients with Acute Myocardial Infarction

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A reduced estimated glomerular filtration rate (eGFR) is a predictor for mortality in patients with acute myocardial infarction (AMI). This study aimed to compare mortality according to the GFR and eGFR calculation methods during long-term clinical follow-ups. Using the Korean Acute Myocardial Infarction Registry-National Institutes of Health Data, 13,021 patients with AMI were included in this study. Patients were divided into the surviving (n=11,503, 88.3%) and deceased (n=1,518, 11.7%) groups. Clinical characteristics, cardiovascular risk factors, and 3-year mortality-related factors were analyzed. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) equations. The surviving group was younger than the deceased group (62.6±12.4 vs. 73.6±10.5 years, $p<0.001$), whereas the deceased group had higher hypertension and diabetes prevalences than the surviving group. A high Killip class was more frequently observed in the deceased group. eGFR was significantly lower in the deceased group (82.2±24.1 vs. 55.2±28.6 ml/min/1.73 m^2, $p<0.001$). Multivariate analysis revealed that low eGFR was an independent risk factor for mortality during the 3-year follow-up. The CKD-EPI equation was more useful for predicting mortality than the MDRD equation (0.766; 95% confidence interval [CI], 0.753-0.779 vs. 0.738; 95% CI, 0.724-0.753; p=0.001). Decreased renal function was a significant predictor of mortality after 3 years in patients with AMI. The CKD-EPI equation was more useful for predicting mortality than the MDRD equation.

Key Words: *Myocardial Infarction; Glomerular Filtration Rate; Renal Insufficiency, Chronic*

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INTRODUCTION

A 2016 World Health Organization report demonstrated that ischemic heart disease (IHD) is the most commoncauseof death worldwide, with approximately 10 million deaths annually, as compared to approximately 7.9 million deaths in 2006.[1]

The leading risk factors for acute myocardial infarction (AMI) include high blood pressure, smoking, diabetes mellitus (DM), dyslipidemia, and chronic kidney disease (CKD). Particularly, a decrease in kidney function may increase morbidity and mortality due to cardiovascular diseases (CVD).[2,3] Patients with CKD show a 10-20-fold increase in death rate from CVD as compared to that of the general population, indicating CKD as an important factor for prognosis and an independent predictor of long-term mortality.[4] Since the estimated glomerular filtration rate (eGFR) is a critical factor for the mortality rate of patients with AMI, it is important to accurately measure it.[5] Recently,

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many studies have suggested that the eGFR Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD\text{-}EPI}$) equation is more accurate than the eGFR Modification of Diet in Renal Disease ($eGFR_{MDRD}$) equation.[6]

Given that reduced eGFR is a predictive factor for mortality in patients with AMI, this study aimed to compare mortality according to the GFR and eGFR calculation methods over a long-term clinical follow-up. Therefore, according to the eGFR calculation formula, we evaluated the factors that predict mortality and the factors that increase prediction accuracy using the Korea Acute Myocardial Infarction Registry of Health (KAMIR-NIH) data.

MATERIALS AND METHODS

1. Study design and data source

This study used data registered in the KAMIR-NIH. Between November 2011 and December 2015, the KAMIR-NIH enrolled a total of 13,104 patients with AMI from 20 hospitals. Of these hospitals, five were located in Seoul, two in Gyeonggi Province, three in Jeolla Province, three in Chungcheong Province, five in Gyeongsang Province, and one each in Gangwon Province and Jeju Island. Among these patients, 13,021 were tested, and 83 patients were excluded from the renal function test. We then classified these patients into the surviving group (11,503) and deceased group (1,518) after a 3-year follow-up study. We confirmed the patients' survival from their hospital records or patient interviews (directly or via phone calls). Those who were alive at the 3rd year after registration with KAMIR were included in the surviving group, and those who died within it were included in the deceased group.

This study was approved by the Institutional Review Board of Chonnam National University Hospital (CNUH 2011-172) and was performed after obtaining consents from all subjects.

2. General characteristics

General characteristics included sex, age, body mass index (BMI), and smoking status. BMI was calculated by dividing the weight (kg) by the squared height (m^2).

3. Clinical characteristics

Clinical characteristics included symptoms, history of CVD, family history of coronary artery disease (CAD), clinical diagnosis, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, hypertension, DM, dyslipidemia, Killip class, and prescribed medications. Symptoms were classified as chest pain and dyspnea based on the main symptoms of AMI, the medical referral from other hospitals, or medical records. Regarding the history of CVDs, we classified them as angina, AMI, and heart failure (HF). Clinical diagnoses were classified into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) based on electrocardiography during visits to the emergency department.[7] Regarding Killip class, the clinical signs of HF were classified into class I (no clinical signs of HF), class II (rales, crackles, or an S3 gallop sound under the lower half of the lung), class III (frank acute pulmonary edema), and class IV (cardiogenic shock; hypotension; and evidence of peripheral vasoconstriction, including oliguria, cyanosis, or sweating).[8]

For medications, we referred to the patients' medical records when they were discharged from the hospital to confirm whether they were prescribed aspirin, beta-blockers, statins, angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB).

4. Laboratory findings

Laboratory findings included blood pressure (BP), hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and creatinine. Blood collection for biochemical analyses was performed during the patients' visit to the emergency department, with the exception of the lipid tests, which were performed after one-day fasting.

5. Coronary arteriographic findings and percutaneous coronary intervention (PCI)

Coronary arteriography (CAG) lesions were classified according to the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA).[9] Coronary blood flow was classified into grade 0 (no flow), grade I (penetration without perfusion), grade II (partial perfusion), or grade III (complete perfusion) based on the thrombolysis in myocardial infarction (TIMI) flow.[10]

6. Measurement of renal function

To assess kidney function, we used eGFR and measured kidney function using the $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$ equations based on the patients' creatinine level, age, sex, and race[11]:

$$eGFR_{CKD\text{-}EPI}\ (mL/min/1.73\ m^2) = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018 \quad [\text{if female}]$$

$$eGFR_{MDRD}\ (mL/min/1.73\ m^2) = 186 \times (Scr)^{-1.154} \times (age)^{-0.203} \times 0.742 \quad [\text{if female}]$$

Kidney function was classified into five stages based on the Kidney Disease Improving Global Outcomes from the National Kidney Foundation: normal or high ($eGFR \geq 90$ mL/min/1.73 m^2), mildly decreased ($60 \leq eGFR > 90$ mL/min/1.73 m^2), mildly to moderately decreased ($45 \leq eGFR > 60$ mL/min/1.73 m^2), moderately to severely decreased ($30 \leq eGFR > 45$ mL/min/1.73 m^2), and severely decreased ($eGFR < 30$ mL/min/1.73 m^2).[11,12]

7. Death confirmation

We referred to the patients' medical records and called

their corresponding hospital to confirm the time and cause of death of each patient within 3 years from hospital discharge. However, if this information was not available from the medical records, we called the patient's family, and we also asked regarding the patient's outpatient visits. Sudden deaths in asymptomatic patients were classified as cardiac deaths. In deceased patients who were transferred to another hospital due to other symptoms, their deaths were classified based only on their final cause of death.

8. Statistical analysis

The IBM SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous variables were plotted as means±standard deviation, whereas categorical variables were described as frequencies and percentages (%). The t-test was used to compare the surviving and deceased groups, with eGFR levels as the continuous variables. The chi-square test was used for categorical variables, considering their relevance.

A Cox regression model was also used to analyze the association between eGFR and death. Sex, age, BMI, and smoking were adjusted in Model 1, and additional adjustments for symptoms, CVD history, clinical diagnosis, Killip class, medications, glucose, HbA1c, TC, TG, HDL-C, hs-CRP, and NT-proBNP were done when we found any significance in this model. In addition, survival analysis was performed between all-cause and CVD mortality, and receiver operating characteristic (ROC) analysis was conducted to compare the area under the curve (AUC) values of $eGFR_{MDRD}$ and $eGFR_{CKD\text{-}EPI}$. All statistical analyses were two-tailed, with significance defined as a value of $p < 0.05$.

RESULTS

1. Baseline characteristics according to mortality

A total of 13,021 patients with AMI were compared, including 11,503 survivors (88.3%) and 1,518 deceased (11.7%). On average, the deceased group was older ($p < 0.001$) and had a lower BMI ($p < 0.001$) than the surviving group. Meanwhile, the smoking rate was significantly higher in the surviving group than that in the deceased group ($p < 0.001$).

The number of patients who experienced chest pain during AMI onset was higher in the surviving group ($p < 0.001$), whereas more patients in the deceased group had difficulty breathing ($p < 0.001$). Moreover, the deceased group had a higher incidence of angina ($p < 0.001$), MI ($p < 0.001$), and HF ($p < 0.001$) than the surviving group. As risk factors of CVD, the deceased group had a significantly higher prevalence of hypertension ($p < 0.001$) and DM ($p < 0.001$) than the surviving group. However, we noted a higher dyslipidemia rate in the surviving group than that in the deceased group. Regarding final diagnosis, the incidence of STEMI was significantly higher (p=0.001) in the surviving group, while that of NSTEMI was significantly higher ($p < 0.001$) in the deceased group. Furthermore, more patients in the deceased group had Killip class II and above ($p < 0.001$), lower BP levels ($p < 0.001$), and higher pulse rates ($p < 0.001$), whereas more patients in the surviving group were prescribed aspirin, beta-blockers, statins, and ACEIs at the time of hospital discharge ($p < 0.001$) (Table 1).

2. Echocardiogram and laboratory findings according to survival

We observed a higher left ventricular ejection fraction (LVEF) and higher levels of blood pressure, HbA1c, hs-CRP, NT-proBNP, and creatinine in the surviving group than those in the deceased group ($p < 0.001$). Contrarily, we observed significantly lower levels of TC, TG, HDL-C, LDL-C, and eGFR in the deceased group than those in the surviving group ($p < 0.001$) (Table 2).

3. Coronary angiographic findings and PCI characteristics according to survival

The frequency of PCI implementation was higher in the surviving group (91.2%) than that in the deceased group (76.9%) ($p < 0.001$). In CAG, the frequency of the left main artery as the target lesion site was higher in the surviving group ($p < 0.001$), while more multivessel diseases were confirmed in the deceased group ($p < 0.001$). Moreover, the deceased group showed more complex lesions based on the ACC/AHA classification and lower TIMI flow before and after PCI than the surviving group (Table 2).

4. Predictive factors for mortality

In a univariate Cox regression analysis, the independent predictors over the 3-year follow-up were $eGFR_{CKD\text{-}EPI}$, high Killip class, low LVEF (<50%), previous MI, stroke, multivessel disease, smoking, DM, old age, hypertension, and dyspnea.

In multivariate analysis, the independent predictors over the 3-year follow-up were $eGFR_{CKD\text{-}EPI}$ (OR 4.098, 95% CI [3.112-5.396], $p < 0.001$), high Killip class (OR 2.026, 95% CI [1.578-2.601], $p < 0.001$), LVEF <50%, (OR 1.609, 95% CI [1.384-1.871], $p < 0.001$), previous MI (OR 1.502, 95% CI [1.223-1.843], $p < 0.001$), stroke (OR 1.479, 95% CI [1.205-1.814], $p < 0.001$), multivessel disease (OR 1.455, 95% CI [1.117-1.895], $p < 0.005$), smoking (OR 1.253, 95% CI [1.065-1.474], $p < 0.006$), DM (OR 1.236, 95% CI [1.062-1.438], $p < 0.006$), and old age (OR 1.067, 95% CI [1.058-1.075], $p < 0.001$) (Table 3).

5. AUC value comparison between $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$

We compared AUC values between $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$, confirming that mortality was significantly higher in $eGFR_{CKD\text{-}EPI}$ than that in $eGFR_{MDRD}$ ($eGFR_{CKD\text{-}EPI}$ 0.766, 95% CI [0.753-0.799] vs. $eGFR_{MDRD}$ 0.738, 95% CI [0.724-0.753]; $p < 0.001$). Furthermore, the AUC values of death due to CVD were higher in $eGFR_{CKD\text{-}EPI}$ than those in $eGFR_{MDRD}$ ($eGFR_{CKD\text{-}EPI}$ 0.775, 95% CI [0.760-0.789] vs.

TABLE 1. Baseline characteristics of the participants

Variable	Total (n=13,021)	Survived (n=11,503)	Deceased (n=1,518)	p-value
Sex, male (%)	9,629 (73.9)	8,686 (75.5)	943 (62.1)	<0.001
Age (years)	63.9±12.7	62.6±12.4	73.6±10.5	<0.001
Current smoking	5,085 (39.1)	4,718 (41.0)	367 (24.2)	<0.001
BMI (kg/m^2)	24.0±3.4	24.2±3.3	22.5±3.6	<0.001
Symptoms (%)				
Chest pain	11,218 (86.2)	10,194 (88.6)	1,024 (67.5)	<0.001
Dyspnea	3,085 (23.7)	2,511 (21.8)	574 (37.8)	<0.001
Previous history				
Previous angina (%)	1,268 (9.7)	1,046 (9.1)	222 (14.6)	<0.001
Previous MI (%)	1,025 (7.9)	807 (7.0)	218 (14.4)	<0.001
Previous HF (%)	211 (1.6)	126 (1.1)	85 (5.6)	<0.001
Family history of CAD (%)	827 (6.5)	776 (6.9)	51 (3.5)	<0.001
Hypertension (%)	6,640 (51.0)	5,673 (49.3)	967 (63.7)	<0.001
Diabetes mellitus (%)	3,732 (28.7)	3,088 (26.8)	644 (42.4)	<0.001
Dyslipidemia (%)	1,467 (11.3)	1,360 (11.8)	107 (7.0)	<0.001
Clinical diagnosis				0.001
STEMI (%)	6,285 (48.3)	5,611 (48.8)	674 (44.4)	
NSTEMI (%)	6736 (51.7)	5,892 (51.2)	844 (55.6)	
Killip class				<0.001
I	10,160 (79.0)	9,438 (82.0)	722 (47.6)	
II	1,126 (8.6)	916 (8.0)	210 (13.8)	
III	973 (7.5)	657 (5.7)	316 (20.8)	
IV	762 (5.9)	492 (4.3)	270 (17.8)	
Systolic BP (mmHg)	130.2±28.9	131.6±28.7	119.6±35.9	<0.001
Diastolic BP (mmHg)	78.7±18.3	79.6±17.5	72.1±22.4	<0.001
Heart rate (/minute)	78.7±19.5	77.8±18.5	85.5±25.0	<0.001
Medication				
Aspirin	12,950 (99.5)	11,468 (99.7)	1,482 (97.6)	<0.001
Beta blockers	10,528 (80.9)	9,668 (84.0)	860 (56.7)	<0.001
Statins	11,768 (90.4)	10,781 (91.6)	987 (65.0)	<0.001
ACEIs	5,983 (45.9)	5,600 (48.7)	383 (25.2)	<0.001
ARBs	4,077 (31.3)	3,623 (31.5)	454 (29.9)	0.210

Values are presented as mean±standard deviation or number (%). ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, HF: heart failure, MI: myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction.

$eGFR_{MDRD}$ 0.751, 95% CI [0.734-0.767]; $p < 0.001$) (Table 4).

6. Baseline characteristics based on $eGFR_{CKD\text{-}EPI}$ values

We classified the general characteristics based on the $eGFR_{CKD\text{-}EPI}$ values, and we obtained the following results: $eGFR_{CKD\text{-}EPI} \geq 90$ mL/min/1.73 m^2, 40.8%; $eGFR_{CKD\text{-}EPI}$ 60-89 mL/min/1.73 m^2, 37.6%; $eGFR_{CKD\text{-}EPI}$ 45-59 mL/min/1.73 m^2, 9.9%; $eGFR_{CKD\text{-}EPI}$ 30-44 mL/min/1.73 m^2, 5.9%; and $eGFR_{CKD\text{-}EPI} < 30$ mL/min/1.73 m^2, 5.8%. A higher $eGFR_{CKD\text{-}EPI}$ value was associated with male sex predominance and higher BMI, height, and smoking rate values. In contrast, $eGFR_{CKD\text{-}EPI}$ decreased with increasing age. Moreover, we identified increased chest pain on AMI onset, family history of CAD, STEMI, SBP, DBP, and dyslipidemia as clinical characteristics associated with $eGFR_{CKD\text{-}EPI}$ values. Prescription of aspirin, beta-blockers, statins, and ACEIs also increased with $eGFR_{CKD\text{-}EPI}$. On the other hand, an increase in dyspnea, angina, MI, history of HF, NSTEMI, pulse, hypertension, DM, total mortality, cardiac death, and Killip class caused a decrease in $eGFR_{CKD\text{-}EPI}$. Furthermore, we demonstrated an increase in the prescription of clopidogrel, ARB, and oral anticoagulants with higher $eGFR_{CKD\text{-}EPI}$ values (Table 5).

7. Echocardiography based on $eGFR_{CKD\text{-}EPI}$ values and laboratory findings

Regarding echocardiography data based on $eGFR_{CKD\text{-}EPI}$ values and laboratory findings, we found a reduction in fasting blood sugar, HbA1c, hs-CRP, NT-proBNP, creatinine, and $eGFR_{MDRD}$, and an increase in LVEF, TC, TG, HDL-C, and LDL-C with increasing $eGFR_{CKD\text{-}EPI}$ values (Table 6).

8. Coronary angiographic and PCI characteristics based on $eGFR_{CKD\text{-}EPI}$ values

We confirmed that lower $eGFR_{CKD\text{-}EPI}$ values were asso-

TABLE 2. Diagnostics findings and procedural characteristics

Variable	Total (n=13,021)	Survived (n=11,503)	Deceased (n=1,518)	p-value
Left ventricular ejection fraction (%)	51.9±11.2	52.7±10.7	44.5±13.4	<0.001
Glucose (mg/dL)	170.0±82.5	165.0±75.9	206.6±114.5	<0.001
Hemoglobin A1c (%)	6.5±1.5	6.5±1.5	6.7±1.6	<0.001
Total cholesterol (mg/dL)	177.8±46.3	180.1±45.4	159.5±49.0	<0.001
Triglycerides (mg/dL)	133.5±114.1	136.3±116.9	110.0±83.4	<0.001
HDL-cholesterol (mg/dL)	42.8±11.9	43.0±11.6	40.9±14.1	<0.001
LDL-cholesterol (mg/dL)	111.7±39.7	113.4±39.2	97.2±40.8	<0.001
hs-CRP (mg/dL)	1.5±5.8	1.3±4.4	4.1±13.0	<0.001
NT-pro BNP (pg/mL)	2646.2±7549.9	1715.2±6092.8	8955.7±12089.3	<0.001
Creatinine (mg/dL)	1.1±1.1	1.0±0.9	1.7±1.7	<0.001
eGFRMDRD (mL/min/1.73 m^2)	87.4±41.2	90.6±39.9	62.6±42.8	<0.001
PCI (%)	11,659 (89.5)	10,491 (91.2)	1,168 (76.9)	<0.001
PCI success rate (%)	11,508 (99.5)	10,388 (99.6)	1,120 (98.1)	<0.001
Target vessel (%)				<0.001
Left main artery	271 (2.3)	187 (1.8)	84 (7.2)	
LAD	5,445 (46.6)	4,903 (46.7)	542 (46.2)	
LCX	2,043 (17.5)	1,866 (17.8)	177 (15.1)	
RCA	3,920 (33.6)	3,551 (33.8)	369 (31.5)	
Number of involved vessels (%)				<0.001
Left main artery	594 (4.7)	462 (4.1)	132 (9.5)	
Single-vessel disease	5,934 (46.5)	5,433 (47.8)	501 (35.9)	
Two-vessel disease	3,528 (27.7)	3,137 (27.6)	391 (28.0)	
Three-vessel disease	2,194 (17.2)	1,897 (16.7)	297 (21.3)	
ACC/AHA type (%)				0.001
A	168 (1.4)	160 (1.5)	8 (0.7)	
B1	1,401 (12.0)	1,283 (12.2)	118 (10.1)	
B2	4,337 (37.1)	3,850 (36.6)	487 (41.7)	
C	5,733 (49.4)	5,214 (49.6)	555 (47.5)	
Pre-PCI TIMI flow (%)				<0.001
0	5,468 (46.9)	4,917 (46.9)	551 (47.2)	
I	1,280 (11.0)	1,145 (10.9)	135 (11.6)	
II	1,800 (15.4)	1,588 (15.1)	212 (19.9)	
III	3,111 (26.7)	2,841 (27.1)	270 (23.1)	
Post-PCI TIMI flow (%)				<0.001
0	47 (0.4)	29 (0.3)	18 (1.5)	
I	57 (0.5)	36 (0.3)	21 (1.8)	
II	312 (2.7)	243 (2.1)	69 (5.9)	
III	11,243 (96.4)	10,183 (97.1)	1,060 (90,8)	

Values are presented as mean±standard deviation or number (%). ACC/AHA: American College of Cardiology/American Heart Association, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, eGFR: estimated glomerular filtration rate, HDL: high density lipoprotein, hs-CRP: high sensitivity C-reactive protein, LAD: left anterior descending artery, LCX: left circumflex artery, LDL: low density lipoprotein, MDRD: Modification of Diet in Renal Disease, NT-proBNP: N-terminal pro-brain natriuretic peptide, PCI: percutaneous coronary intervention, RCA: Right coronary artery, TIMI: thrombolysis in myocardial infarction.

ciated with a lower frequency of PCI implementation, whereas higher $eGFR_{CKD\text{-}EPI}$ values were associated with a higher success rate of PCI. In CAG, low $eGFR_{CKD\text{-}EPI}$ values were associated with a higher frequency of the left main coronary artery as the target vessel. Moreover, higher $eGFR_{CKD\text{-}EPI}$ values were associated with more multivessel diseases and significant differences in TIMI flow before and after PCI and in vessel lesions, according to the ACC/AHA classification (Table 7).

9. Association between all-cause mortality and CVD mortality by $eGFR_{CKD\text{-}EPI}$ level

To determine the association between all-cause mortality and CVD mortality by $eGFR_{CKD\text{-}EPI}$ level, we first adjusted for sex, age, BMI, and smoking (Model 1). We also adjusted for SBP, pulse, hypertension, DM, dyslipidemia, chest pain, dyspnea, angina, MI, HF, family history of CAD, STEMI, NSTEMI, Killip class, aspirin, clopidogrel, beta-blockers, statins, ACEIs, ARB, oral anticoagulants, blood sugar, HbA1c, TC, TG, HDL-C, hs-CRP, and NT-proBNP when indicated. On analysis, we found that total

TABLE 3. Cox regression analysis for independent predictors of mortality

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
$eGFR_{CKD-EPI}$	16.725	13.983-20.003	<0.001	4.098	3.112-5.396	<0.001
High Killip class	5.860	5.043-6.809	<0.001	2.026	1.578-2.601	<0.001
LVEF (<50%)	2.731	2.436-3.061	<0.001	1.609	1.384-1.871	<0.001
Previous MI	2.120	1.833-2.452	<0.001	1.502	1.223-1.843	<0.001
Stroke	2.571	2.221-2.978	<0.001	1.479	1.205-1.814	<0.001
Age	1.081	1.075-1.086	<0.001	1.067	1.058-1.075	<0.001
$eGFR_{MDRD}$	12.723	10.769-15.032	<0.001	3.736	1.627-8.576	0.002
Current smoking	0.462	0.407-0.525	<0.001	1.253	1.065-1.474	0.006
Diabetes mellitus	1.971	1.776-2.188	<0.001	1.236	1.062-1.438	0.006
Multi-vessel disease	2.747	2.244-3.361	<0.001	1.455	1.117-1.895	0.005
Hypertension	1.789	1.606-1.992	<0.001	0.963	0.825-1.123	0.630
Dyspnea	2.103	1.891-2.339	<0.001	0.894	0.758-1.054	0.183

CI: confidence interval, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, eGFR: estimated glomerular filtration rate.

TABLE 4. Comparison of AUCs between $eGFR_{CKD-EPI}$ and $eGFR_{MDRD}$

	All cause death	CVD death
$eGFR_{MDRD}$	0.738 (0.724-0.753)	0.751 (0.734-0.767)
$eGFR_{CKD-EPI}$	0.766 (0.753-0.779)	0.775 (0.760-0.789)
p-value	<0.001	<0.001

Values are presented as AUC (95% CI). CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, CVD: cardiovascular disease, eGFR: estimated glomerular filtration rate, MDRD: Modification of Diet in Renal Disease.

mortality was significantly higher at low $eGFR_{CKD-EPI}$ levels (OR 1.62, 95% CI [0.95-2.76]; OR 2.06, 95% CI [1.14-3.74]; OR 2.04, 95% CI [1.10-3.79]; OR 3.93, 95% CI [2.07-7.45]). Regarding cardiac mortality, we confirmed that the mortality rate was significantly higher at low $eGFR_{CKD-EPI}$ levels (OR 1.63, 95% CI [0.86-3.11]; OR 2.42, 95% CI [1.19-4.90]; OR 2.65, 95% CI [1.30-5.42]; OR 5.72, 95% CI [2.83-11.59]) (Table 8).

9. Kaplan-Meier survival analysis by $eGFR_{CKD-EPI}$ level

Results of the Kaplan-Meier survival analysis using $eGFR_{CKD-EPI}$ levels are shown in Figs. 1 and 2. Indeed, we confirmed significant differences in all-cause ($p<0.001$, Fig. 1) and cardiac mortality according to eGFR levels ($p<0.001$, Fig. 2).

DISCUSSION

This study demonstrated that independent predictors for mortality in patients with AMI included $eGFR_{CKD-EPI}$, high Killip class, LVEF (<50%), history of MI, stroke, multivessel diseases, smoking, DM, and age. Particularly, the mortality rate increased as eGFR decreased, even after correcting for several variables. In addition, the CKD-EPI equation had a higher AUC value than that of the MDRD equation.

Major risk factors for CAD include smoking, hypertension, DM, and dyslipidemia. Thus, it is critical to control these risk factors for the prevention and treatment of CAD. Paradoxically, smokers showed a lower mortality rate after infarction, although smoking is a risk factor for AMI. This is known as the "smoker's paradox".[13,14] However, this study showed that smoking was an independent predictor of death after the 3-year follow-up.

This study also showed an inverse relationship between eGFR and all-cause and cardiac mortality. Overall, the association between high all-cause and cardiac mortality and low eGFR levels was significant. The Framingham Heart Study, in which 6,223 patients classified into the normal and mild groups were tracked for 11 years, reported that the mildly decreased group had a 1.7-fold increase in cardiac mortality than the normal group.[15] A large-scale study in 2004, in which 1,120,295 people were followed for 3 years, showed that decreased kidney function was an independent predictive factor for increasing cardiac morbidity and mortality, especially with a severe reduction in eGFR.[15] These studies showed similar findings to that of the present study.

Chronic kidney disease is known to increase the risk of atherosclerosis, endothelial cell dysfunction, and thrombosis due to anemia, oxidative stress, nitric oxide synthesis inhibition, inflammation, and activation of coagulation factors.[16,17] According to a previous study, in which 4,484 healthy adults were followed up for approximately 8.6 years, low eGFR increased the rate of AMI by three times and increased the mortality rate after diagnosis.[18]

Different eGFR evaluation methods lead to various distributions of eGFR and CKD prevalence.[19] Plasma creatinine level is the most common index used to evaluate kidney function and is affected by individual muscle mass. Therefore, this should be carefully utilized, especially in women and older people, since their creatinine levels are within the normal range despite the reduction in eGFR.[20]

TABLE 5. Baseline characteristics in subjects according to the $eGFR_{CKD-EPI}$ levels

Variable	$eGFR_{CKD-EPI}$					p-value
	<30 (n=761)	30-44 (n=768)	45-59 (n=1,283)	60-89 (n=4,899)	≥90 (n=5,310)	
Sex, male (%)	432 (56.8)	437 (56.9)	820 (63.9)	3,606 (73.6)	4,334 (81.6)	<0.001
Age (years)	71.4±11.1	74.5±9.8	71.7±10.3	66.9±11.7	56.8±10.6	<0.001
BMI (kg/m^2)	23.1±3.5	23.4±3.6	23.5±3.5	23.9±3.3	24.4±3.3	<0.001
Current smoking (%)	132 (17.3)	156 (20.3)	333 (26.0)	1,680 (34.3)	2,784 (52.4)	<0.001
Symptom						
Chest pain (%)	468 (61.5)	553 (72.0)	1,025 (79.9)	4,254 (86.8)	4,918 (92.6)	<0.001
Dyspnea (%)	359 (47.2)	326 (42.4)	413 (32.2)	1,152 (23.5)	835 (15.7)	<0.001
Previous history						
Previous angina (%)	127 (16.7)	118 (15.4)	189 (14.7)	496 (10.1)	338 (6.4)	<0.001
Previous MI (%)	124 (16.3)	89 (11.6)	139 (10.8)	364 (7.4)	309 (5.8)	<0.001
Previous HF (%)	38 (5.0)	43 (5.6)	42 (3.3)	57 (1.2)	31 (0.6)	<0.001
Hypertension (%)	605 (79.5)	576 (75.0)	841 (65.5)	2,607 (53.2)	2,011 (37.9)	<0.001
Diabetes mellitus (%)	494 (64.9)	380 (49.5)	498 (38.8)	1,238 (25.3)	1,122 (21.1)	<0.001
Dyslipidemia (%)	73 (9.6)	81 (10.5)	153 (11.9)	559 (11.4)	601 (11.3)	0.054
Clinical diagnosis						<0.001
STEMI (%)	229 (30.1)	332 (43.2)	634 (49.4)	2,520 (51.4)	2,570 (48.4)	
NSTEMI (%)	532 (69.9)	436 (56.8)	649 (50.6)	2,379 (48.6)	2,740 (51.6)	
Systolic BP (mmHg)	127.6±35.6	123.1±34.9	123.6±33.2	130.2±30.1	133.1±26.4	<0.001
Diastolic BP (mmHg)	74.5±20.8	72.5±21.2	73.9±19.5	78.3±18.2	81.6±16.4	<0.001
Heart rate (/minute)	85.9±23.6	83.5±24.0	80.4±24.3	77.3±19.2	77.9±16.6	<0.001
Death by CVD (%)	267 (35.1)	182 (23.7)	188 (14.7)	331 (6.8)	128 (2.4)	<0.001
Death by any cause (%)	345 (45.3)	240 (31.3)	262 (20.4)	475 (9.7)	196 (3.7)	<0.001
Killip class (%)						<0.001
I	358 (47.0)	396 (51.6)	778 (60.6)	3,831 (78.2)	4,796 (90.3)	
II	131 (17.2)	108 (14.1)	181 (14.1)	441 (9.0)	265 (5.0)	
III	176 (23.1)	149 (19.4)	176 (13.7)	337 (6.9)	135 (2.5)	
IV	96 (12.6)	115 (15.0)	148 (11.5)	289 (5.9)	114 (2.1)	
Medication						<0.001
Aspirin	749 (98.4)	761 (99.1)	1,275 (99.4)	4,873 (99.5)	5,292 (99.7)	<0.001
Beta blockers	514 (67.5)	543 (70.7)	968 (75.4)	4,026 (82.2)	4,477 (84.3)	<0.001
Statins	548 (72.0)	596 (77.6)	1,096 (85.4)	4,495 (91.8)	5,033 (94.8)	<0.001
ACEIs	160 (21.0)	280 (36.5)	573 (44.7)	2,441 (49.8)	2,529 (47.6)	<0.001
ARBs	278 (36.5)	232 (30.2)	407 (31.7)	1,465 (29.9)	1,695 (31.9)	0.004

Values are presented as mean±standard deviation or number (%). ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, BMI: body mass index, BP: blood pressure, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, CVD: cardiovascular disease, eGFR: estimated glomerular filtration rate, HF: heart failure, MI: myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction.

Notably, the MDRD equation only considers white and black individuals, resulting in higher than actual eGFR levels in Asians. Even when the eGFR value is within the normal range or is slightly reduced, its utility is limited by the lack of accuracy.[21] Thus, the CKD-EPI equation was developed to address this discrepancy.[22,23] A previous study showed that the diagnosis rate of CKD with an eGFR level of 60 mL/min/1.73 m^2 dropped from 11.5% using MDRD to 13% when re-classified using CKD-EPI.[24]

Chronic kidney disease is often asymptomatic in the early stages and, if not detected early, will result in the loss of kidney function and CVD complications. As such, accurate diagnosis and management of the kidneys are necessary. In this study, we estimated eGFR using both MDRD and CKD-EPI to evaluate the severity of CKD. The groups were then divided by eGFR values based on useful and reliable CKD-EPI evaluations in the guidelines.[11] Moreover, we utilized MDRD and CKD-EPI and obtained ROC-AUC scores of 0.766 and 0.755 for multiorgan failure death and cardiogenic death, respectively. This proved that CKD-EPI was more meaningful and useful than MDRD. Previous studies have also compared $eGFR_{CKD-EPI}$ and $eGFR_{MDRD}$ results to the AUC scores of patients with AMI, which were demonstrated to be more useful predictors for post-AMI mortality.[25]

Patients with CKD are also prone to hypertension, DM, and anemia.[26] In this study, it was shown that patients with a low eGFR were more likely to have hypertension, DM, history of angina, MI, and HF. The Killip class, one of the risk factors that exacerbate clinical outcomes after AMI, has

Table 6. Laboratory and echocardiographic findings of the subjects according to the $eGFR_{CKD\text{-}EPI}$ levels

Variable	$eGFR_{CKD\text{-}EPI}$					p-value
	<30 (n=761)	30-44 (n=768)	45-59 (n=1,283)	60-89 (n=4,899)	≥90 (n=5,310)	
LVEF (%)	45.2±12.8	46.6±13.6	49.7±12.5	51.9±10.8	54.0±1.0	<0.001
Glucose (mg/dL)	220±135.0	213.9±112.3	196.2±96.8	165.3±72.3	154.1±63.8	<0.001
Hg A_{1c} (%)	6.9±1.7	6.8±1.4	6.6±1.5	6.4±1.4	6.4±1.5	<0.001
Total cholesterol (mg/dL)	153.3±51.1	163.8±46.1	171.0±46.6	177.8±44.5	184.8±45.3	<0.001
Triglycerides (mg/dL)	118.7±86.7	120.1±88.7	128.1±107.8	128.2±98.4	143.3±132.5	<0.001
HDL-cholesterol (mg/dL)	39.3±13.4	41.4±13.2	42.3±12.5	43.3±11.8	43.0±11.3	<0.001
LDL-cholesterol (mg/dL)	89.6±39.5	97.4±39.6	103.8±37.9	111.8±39.1	117.7±38.9	<0.001
hs-CRP (mg/dL)	4.8±12.1	3.1±9.6	2.1±9.6	1.2±3.3	0.9±3.9	<0.001
NT-pro BNP (pg/mL)	17,997.5±20,754.4	6,349.5±8,129.6	3,487.6±6,297.4	1,378.3±3,037.1	634.3±1,682.2	<0.001
Creatinine (mg/dL)	4.2±3.0	1.6±0.3	1.2±0.2	1.0±0.2	0.7±0.2	<0.001
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	18.5±8.7	41.3±4.5	55.8±4.6	79.8±11.8	118.6±42.0	<0.001

$eGFR_{CKD\text{-}EPI}$: estimated glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration, $eGFR_{MDRD}$: estimated galomerular filtration rate Modification of Diet in Renal Disease, LVEF: left ventricular ejection fraction, HDL: high density lipoprotein, hs-CRP: high sensitivity C-reactive protein, LDL: low density lipoprotein, NT-proBNP: N-terminal pro-brain natriuretic peptide.

Table 7. Coronary angiographic findings and procedural characteristics of the subjects according to the $eGFR_{CKD\text{-}EPI}$ levels

Variable	$eGFR_{CKD\text{-}EPI}$					p-value
	<30 (n=761)	30-44 (n=768)	45-59 (n=1,283)	60-89 (n=4,899)	≥90 (n=5,310)	
PCI (%)	584 (76.7)	646 (84.1)	1,123 (87.5)	4,465 (91.1)	4,841 (91.2)	<0.001
PCI success rate (%)	564 (98.3)	624 (98.9)	1,105 (99.3)	4,414 (99.5)	4,801 (99.7)	<0.001
Target vessel (%)						<0.001
Left main artery	32 (5.5)	34 (5.3)	34 (3.0)	82 (1.8)	89 (1.8)	
LAD	239 (40.9)	282 (43.7)	493 (43.8)	2,045 (45.7)	2,386 (49.2)	
LCX	95 (16.2)	88 (13.6)	170 (15.1)	765 (17.1)	925 (19.1)	
RCA	219 (37.4)	242 (37.5)	429 (38.1)	1,580 (35.3)	1,450 (29.9)	
Number of involved vessels (%)						<0.001
Left main artery	67 (9.5)	68 (9.4)	68 (5.5)	205 (4.2)	186 (3.5)	
Single-vessel disease	224 (31.9)	219 (30.3)	482 (38.9)	2,224 (46.1)	2,785 (52.9)	
Two-vessel disease	199 (28.3)	221 (30.6)	365 (29.5)	1,358 (28.2)	1,385 (26.3)	
Three-vessel disease	180 (25.6)	193 (26.7)	285 (23.0)	869 (18.0)	667 (12.7)	
ACC/AHA type (%)						0.001
A	9 (1.5)	4 (0.6)	13 (1.2)	59 (1.3)	83 (1.7)	
B1	63 (10.8)	85 (13.2)	164 (14.6)	553 (12.4)	526 (11.1)	
B2	230 (39.3)	233 (36.1)	395 (35.1)	1,581 (35.4)	1,898 (39.1)	
C	283 (48.4)	324 (50.2)	554 (49.2)	2,279 (51.0)	2,333 (48.1)	
Pre-PCI TIMI flow (%)						<0.001
0	215 (28.3)	285 (37.1)	511 (39.8)	2,124 (43.4)	2,347 (44.2)	
I	77 (10.1)	91 (11.8)	147 (11.5)	556 (11.3)	409 (7.7)	
II	119 (15.6)	92 (12.0)	184 (14.3)	676 (13.8)	729 (13.7)	
III	174 (22.9)	178 (23.2)	284 (22.1)	1,116 (22.8)	1,365 (25.7)	
Post-PCI TIMI flow (%)						<0.001
0	7 (0.9)	6 (0.8)	6 (0.5)	16 (0.3)	12 (0.2)	
I	5 (0.7)	8 (1.0)	5 (0.4)	20 (0.4)	19 (0.4)	
II	27 (3.5)	25 (3.3)	46 (3.6)	118 (2.4)	96 (1.8)	
III	546 (71.7)	607 (79.0)	1,069 (83.3)	4,318 (88.1)	4,723 (88.9)	

Values are presented as mean±standard deviation or number (%). ACC/AHA: American College of Cardiology/American Heart Association, $eGFR_{CKD\text{-}EPI}$: estimated glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration, LAD: left anterior descending artery, LCX: left circumflex artery, PCI: percutaneous coronary intervention, RCA: right coronary artery, TIMI: thrombolysis in myocardial infarction.

TABLE 8. Adjusted hazard ratios for all-cause mortality and cardiovascular disease mortality according to the $eGFR_{CKD-EPI}$ levels

$eGFR_{CKD-EPI}$		Death/person-years	Model 1	Model 2
All-cause mortality	≥90	196/5,545,443	1	1
	60-89	475/4,904,537	1.55 (1.26-1.92)	1.62 (0.95-2.76)
	45-59	262/1,154,828	2.61 (2.04-3.33)	2.06 (1.14-3.74)
	30-44	240/594,367	3.90 (3.02-5.04)	2.04 (1.10-3.79)
	<30	345/502,802	8.21 (6.52-10.34)	3.93 (2.07-7.45)
CVD mortality	≥90	128/5,545,334	1	1
	60-89	331/4,904,098	1.62 (1.25-2.10)	1.63 (0.86-3.11)
	45-59	188/1,155,017	2.34 (1.74-3.15)	2.42 (1.19-4.90)
	30-44	182/594,052	3.95 (2.92-5.33)	2.65 (1.30-5.42)
	<30	267/501,934	8.00 (6.07-10.54)	5.72 (2,83-11.59)

Model 1 is adjusted for sex, age, body mass index, and current smoking. Model 2 is adjusted for the variables in Model 1 plus systolic blood pressure, diastolic blood pressure, heart rate, hypertension, diabetes mellitus, dyslipidemia, chest pain, dyspnea, previous angina, previous myocardial infarction, previous heart failure, family history of coronary artery disease, final diagnosis, Killip class, medication (aspirin, clopidogrel, beta blockers, statins, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, oral anticoagulants), glucose, hemoglobin A_{1c}, total cholesterol, triglycerides and high density lipoprotein, high sensitivity C-reactive protein, and N-terminal pro-brain natriuretic peptide. CVD: cardiovascular disease, $eGFR_{CKD-EPI}$: estimated glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration.

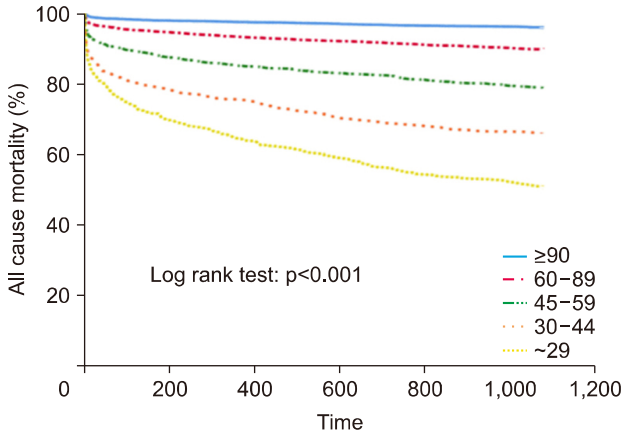

FIG. 1. Kaplan-Meier curve of all cause mortality according to eGFR levels during three-year clinical follow-up. Three-year mortality was significantly different according to levels of eGFR. eGFR: estimated glomerular filtration rate, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

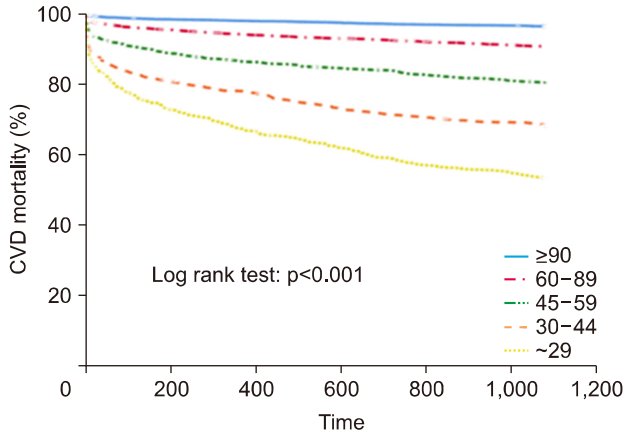

FIG. 2. Kaplan-Meier curve of cardiovascular mortality according to eGFR levels during three-year clinical follow-up. Three-year mortality was significantly different according to levels of eGFR. CVD: cardio vascular disease, eGFR: estimated glomerular filtration rate, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

been reported to be high in groups with a low eGFR.[27,28] Aspirin, beta-blockers, statins, and ACEIs are also commonly used to decrease the recurrence of CVD and increase survival rates.[29] Similarly, the prescription rate of these drugs in the present study was low for patients with decreased eGFR levels, which was comparable to the results of previous studies.[29] Other studies have also shown that lipid-lowering treatment does not reduce the risk of cardiovascular mortality in patients with advanced CKD.[30]

Despite these findings, this study has some limitations. First, there was no prior investigation regarding prescriptions that may affect the kidney on admission. Second, the study included patients with acute kidney injury, since serum creatinine levels were measured after patients' hospital admission. Finally, the study was conducted using a retrospective methodology. Nevertheless, this study involved 20 universities and teaching hospitals, showing sufficient basic data of patients with AMI in Korea. In addition, the results of the study are meaningful, as this study identified the differences in GFR depending on the equation used to evaluate it.

In conclusion, the decrease in eGFR was a significant predictor of mortality in patients with AMI 3 years after discharge. Moreover, the CKD-EPI equation for eGFR was more useful than the MDRD equation in predicting mortality. Indeed, we believe that prospective studies are necessary to compare the differences in the predictive factors for mortality in patients with AMI depending on eGFR evaluation methods.

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CONFLICT OF INTEREST STATEMENT

None declared.

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