Original Paper

Contrast Volume/Raw eGFR Ratio for Predicting Contrast-Induced Acute Kidney Injury in Patients Undergoing Percutaneous Coronary Intervention for Myocardial Infarction

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Key Words

Estimated glomerular filtration rate · Body surface area normalization · Contrast-induced acute kidney injury

Abstract

Background: Considering that contrast medium is excreted through the whole kidney in a similar manner to drug excretion, the use of raw estimated glomerular filtration rate (eGFR) rather than body surface area (BSA)-normalized eGFR is thought to be more appropriate for evaluating the risk of contrast-induced acute kidney injury (CI-AKI). **Methods:** This study included 2,189 myocardial infarction patients treated with percutaneous coronary intervention. Logistic regression analysis was performed to identify the independent risk factors. We used receiver-operating characteristic (ROC) curves to compare the ratios of contrast volume (CV) to eGFR with and without BSA normalization in predicting CI-AKI. **Results:** The area under the curve (AUC) of the ROC curve for the model including all the significant variables such as diabetes mellitus, left ventricular ejection fraction, preprocedural glucose, and the CV/raw mod-

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ification of diet in renal disease (MDRD) eGFR ratio was 0.768 [95% confidence interval (CI), 0.720–0.816; $p < 0.001$]. When the CV/raw MDRD eGFR ratio was used as a single risk value, the AUC of the ROC curve was 0.650 (95% CI, 0.590–0.711; $p < 0.001$). When the CV/MDRD eGFR ratio with BSA normalization ratio was used, the AUC of the ROC curve further decreased to 0.635 (95% CI, 0.574–0.696; $p < 0.001$). The difference between the two AUCs was significant ($p = 0.002$). **Conclusions:** Raw eGFR is a better predictor for CI-AKI than BSA-normalized eGFR.

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Introduction

Recent studies have demonstrated that the ratio of contrast volume (CV) to either estimated glomerular filtration rate (eGFR) or creatinine clearance (eClCr) can be used as a single risk predictor for contrast-induced acute kidney injury (CI-AKI), since this ratio pharmacokinetically means the area under the curve (AUC) representing the systemic exposure of a contrast agent to the body [1, 2]. When dealing with pharmacokinetic issues, it is more appropriate to use the raw eGFR in absolute numbers (ml/min) individualized with the removal of body surface area (BSA) normalization. However, some studies have taken the CV/BSA-normalized eGFR (ml/min/1.73 m²) ratio for predicting CI-AKI, whereas others have applied eClCr (ml/min) using the Cockcroft-Gault (CG) formula [3–6]. When drug dosing is adjusted in patients with chronic kidney disease, it is recommended to use eClCr derived from the CG formula or eGFR without BSA normalization [7, 8].

We hypothesized that raw eGFR is more appropriate for predicting CI-AKI than BSA-normalized eGFR and conducted this observational cohort study.

Methods

Subjects

Data of the study population was extracted from the Catholic Medical Center Percutaneous Coronary Intervention (COACT) Registry, a prospective multicenter, all-comer-based registry of patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents between January 1, 2004 and December 31, 2009 in eight hospitals affiliated with the Catholic Medical Center in South Korea. Among the 4,807 patients with follow-up laboratory data more than 2 weeks after index PCI, patients with end-stage renal disease and those on hemodialysis or peritoneal dialysis ($n = 138$) as well as renal transplant recipients ($n = 36$) were excluded. A total of 4,633 patients were identified, and 2,189 myocardial infarction (MI) patients were included in our analysis.

All the patients received preprocedure intravenous hydration with half-normal saline at the rate of 1 ml/kg body weight (BW) per hour once MI was diagnosed. The contrast dose was left to the discretion of the interventional cardiologist. After exposure to contrast medium, the patients again received half-normal saline intravenously at a rate of 1 ml/kg/h for 12 h. This hydration rate was reduced in patients with decreased left ventricular ejection fraction (LVEF) or overt heart failure. The contrast agent used for primary PCI was iodixanol, an isosmolar nonionic dimer (Visipaque; GE Healthcare, Princeton, N.J., USA). The registry was approved by the Institutional Review Board of the Catholic Medical Center of South Korea (IRB No. XC11RIMI0107K).

Definition

CI-AKI was defined as an absolute increase of serum creatinine (SCr) by >0.3 mg/dl or a relative increase of SCr by $>50\%$, in accordance with the Acute Kidney Injury Network criteria. CI-AKI was diagnosed based on pre- and post-PCI SCr measurements. The pre-PCI SCr level was defined as that measured just before the procedure. The post-PCI SCr level was defined as the highest level measured within 7 days of PCI. BSA was calculated using the following Mosteller formula:

$$\text{BSA}(\text{m}^2) = \sqrt{\frac{\text{height}(\text{cm}) \times \text{weight}(\text{kg})}{3,600}}$$

Raw eGFR was calculated using the following equation:

$$\text{Raw eGFR} = \text{eGFR with BSA normalization} \times \frac{\text{BSA}}{1.73}.$$

Modification of diet in renal disease (MDRD) eGFR (ml/min/1.73 m²) was calculated using the following equation: eGFR = 175 × SCr (mg/dl)^{-1.154} × (age)^{-0.203} × (0.742 if female). Underweight and overweight were defined as having a body mass index (BMI) <18.5 and >25.0, respectively.

Collection of Clinical and Laboratory Data

Variables included in the analysis were demographics (age, gender, height, and BW), medical history [presence of diabetes mellitus (DM), hypertension, and previous cerebrovascular accident (CVA)], smoking status, LVEF by echocardiography, laboratory findings (lipid profile, hemoglobin, preprocedural plasma glucose level measured in the emergency department before PCI, and pre- and post-PCI SCr levels measured during hospitalization), and CV used during PCI.

Statistical Analyses

Continuous variables are presented as means ± SD and were compared using the t test for independent samples. Variables that were not normally distributed are presented as medians and interquartile ranges and were compared with the Mann-Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Binary logistic regression for estimating the hazard ratio and 95% confidence interval (CI) was used to identify the predictive factors for the development of CI-AKI. The variables with a variance inflation factor >10 were considered to have a multicollinearity problem. Analyses of receiver-operating characteristic (ROC) curves were conducted for risk variables for CI-AKI. ROC curves were then compared to determine which one was better for predicting CI-AKI. All p values were two-tailed, and p values <0.05 were considered significant. Statistical analyses were performed using SPSS version 15.0 for Windows (SPSS, Chicago, Ill., USA) and the MedCalc version 11.6.1.0 statistical package (Med-Calc Software, Mariakerke, Belgium).

Results

Baseline Demographic, Clinical, and Laboratory Profiles

Of 2,189 patients, 157 (7.2%) developed CI-AKI according to our definition. The patients in the CI-AKI group were older, and there were more female patients in this group. Height and BW were lower in the CI-AKI group. The CI-AKI group had a higher prevalence of DM, hypertension, and CVA. LVEF and hemoglobin were lower, while preprocedural plasma glucose levels were higher in the CI-AKI group than in the non-CI-AKI group. A comparison of lipid profiles between the two groups showed that both high-density lipoprotein cholesterol (HDL-C) and non-HDL-C levels were lower in the CI-AKI group. The CV and CV/BW were not significantly different between two groups. Preprocedural MDRD eGFR and raw eGFR (MDRD eGFR without BSA normalization) were lower in the CI-AKI group than in the non-CI-AKI group, with the difference in raw eGFR being larger. The CV/MDRD eGFR ratio was significantly larger in the CI-AKI group, and the CV/raw MDRD eGFR ratio was also larger compared to that in the non-CI-AKI group (table 1).

Predictors of Developing CI-AKI

Univariate and multivariate logistic regression analyses were performed to assess the effects of variables on CI-AKI development. Potential confounders (features that differed between the two groups) were included. Variables with a p value <0.1 in the univariate analyses were included in the multivariate model. No variables, including the CV/BW and CV/

Table 1. Baseline characteristics of the groups with and without CI-AKI

	Total (n = 2189)	CI-AKI group (n = 157)	Non-CI-AKI group (n = 2,032)	p value
Age, years	62 (53–71)	68 (57–74)	62 (52–71)	<0.001 [†]
Female gender	928 (42.4)	83 (52.9)	845 (41.6)	0.006
Height, cm	165.0 (159.0–170.0)	163.0 (155.0–168.0)	165.0 (159.0–170.0)	0.001 [†]
BW, kg	65.0 (58.0–73.0)	63.0 (55.0–68.5)	65.0 (58.0–73.0)	<0.001 [†]
BSA, m ²	1.72±0.18	1.67±0.18	1.73±0.18	<0.001
DM	719 (32.8)	91 (58.0)	628 (30.9)	<0.001
Hypertension	1,069 (48.8)	101 (64.3)	968 (47.6)	<0.001
Smoking	940 (42.9)	57 (36.3)	883 (43.5)	0.08
History of CVA	143 (6.5)	22 (14.0)	121 (6.0)	<0.001
LVEF, %	55.0 (46.6–60.0)	49.0 (40.0–55.0)	55.0 (47.0–60.4)	<0.001 [†]
Hemoglobin, g/dl	13.9 (12.6–15.3)	13.0 (11.0–14.4)	14.0 (12.7–15.3)	<0.001 [†]
Preprocedural				
plasma glucose, mg/dl	136.0 (112.0–186.0)	171.0 (124.5–239.8)	135.7 (112.0–182.0)	<0.001 [†]
HDL-C, mg/dl	40.0 (34.0–46.0)	38.0 (32.0–45.0)	40.0 (34.0–46.0)	0.013 [†]
Non-HDL-C, mg/dl	136.0 (111.0–162.0)	130.0 (103.0–153.0)	136.0 (111.0–163.0)	0.019 [†]
CV, ml	250.0 (200.0–350.0)	250.0 (190.0–384.8)	250.0 (200.0–350.0)	0.831 [†]
CV/BW, ml/kg	4.0 (2.8–5.5)	4.3 (2.8–6.1)	3.9 (2.8–5.5)	0.091 [†]
Preprocedural MDRD				
eGFR, ml/min/1.73 m ²	70.6 (58.4–83.4)	57.3 (35.1–74.1)	71.3 (59.5–84.0)	<0.001 [†]
Preprocedural raw				
MDRD eGFR, ml/min	70.6 (56.8–85.1)	54.9 (32.8–71.7)	71.6 (58.3–86.2)	<0.001 [†]
CV/MDRD eGFR	3.64 (2.56–5.34)	4.65 (2.85–8.30)	3.58 (2.55–5.23)	<0.001 [†]
CV/raw MDRD eGFR	3.67 (2.56–5.40)	4.99 (3.04–9.24)	3.61 (2.54–5.22)	<0.001 [†]

Values are presented as numbers with percentages in parentheses, means ± SD, or medians with interquartile ranges in parentheses, as appropriate. [†] Calculated using the nonparametric Mann-Whitney U test.

raw MDRD eGFR ratios, were found to have multicollinearity. In the multivariate analysis, DM, LVEF, preprocedural plasma glucose, and the CV/raw MDRD eGFR ratio were found to be the independent risk factors for development of CI-AKI (table 2).

Comparison of ROC Curves

The Hosmer-Lemeshow test of the established model based on DM, LVEF, preprocedural glucose, and the CV/raw MDRD eGFR ratio showed a satisfactory goodness of fit ($p = 0.989$). The AUC of the ROC curve for this model including all the significant variables was 0.768 (95% CI, 0.720–0.816; $p < 0.001$), and the ROC curve exhibited 56.5% sensitivity and 85.3% specificity at a cutoff level of 0.0901.

When the CV/raw MDRD eGFR ratio was used as a single risk value, the AUC of the ROC curve decreased to 0.650 (95% CI, 0.590–0.711; $p < 0.001$), which was a significant difference ($p = 0.001$) compared with the full-scale model. When the CV/MDRD eGFR with BSA normalization ratio was used, the AUC further decreased to 0.635 (95% CI, 0.574–0.696; $p < 0.001$). The difference between the two AUCs for the ratios of CV/raw MDRD eGFR and the CV/MDRD eGFR with BSA normalization ratios was significant ($p = 0.002$; fig. 1).

Since the differences between the eGFRs calculated with and without BSA normalization are more marked in underweight or overweight persons than in persons within the normal range [9], we extracted 911 underweight and overweight patients from the whole study population. In this population, the AUC of the ROC curve of the CV/raw MDRD eGFR ratio for

Table 2. Univariate and multivariate logistic regression model analyses of CI-AKI

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.025 (1.011–1.039)	<0.001	0.994 (0.973–1.016)	0.617
Female gender	1.576 (1.138–2.182)	0.006	0.895 (0.553–1.447)	0.651
BW	0.971 (0.956–0.987)	<0.001	0.977 (0.953–1.001)	0.063
DM	3.083 (2.215–4.290)	<0.001	2.376 (1.459–3.868)	0.001
Hypertension	1.982 (1.414–2.780)	<0.001	1.269 (0.810–1.989)	0.299
Smoking	0.742 (0.530–1.039)	0.082	0.966 (0.610–1.529)	0.883
History of CVA	2.574 (1.582–4.187)	<0.001	1.738 (0.911–3.314)	0.093
LVEF	0.951 (0.937–0.966)	<0.001	0.963 (0.945–0.981)	<0.001
Hemoglobin	0.768 (0.712–0.828)	<0.001	0.906 (0.807–1.017)	0.093
Preprocedural plasma glucose	1.005 (1.004–1.007)	<0.001	1.003 (1.001–1.005)	0.015
HDL-C	0.976 (0.960–0.993)	0.005	0.988 (0.968–1.008)	0.222
Non-HDL-C	0.995 (0.990–0.999)	0.013	1.000 (0.995–1.005)	0.988
CV/BW	1.077 (1.002–1.158)	0.045	0.946 (0.840–1.066)	0.365
CV/raw MDRD eGFR	1.115 (1.077–1.155)	<0.001	1.073 (1.019–1.131)	0.008

HR = Hazard ratio.

Fig. 1. Comparison of the ROC curves of the model including all the significant variables as well as the CV/raw MDRD eGFR and the CV/MDRD eGFR ratios.

predicting CI-AKI was 0.655 (95% CI, 0.566–0.744; $p < 0.001$), which is almost the same value compared with that of the whole population, whereas the AUC of the ROC curve of the CV/MDRD eGFR with BSA normalization ratio was 0.628 (95% CI, 0.535–0.72; $p = 0.003$), which is lower than that of the whole population. The difference between the two AUCs was significant ($p = 0.006$; fig. 2).

Fig. 2. Comparison of the ROC curves of the CV/raw MDRD eGFR and the CV/MDRD eGFR ratios of the underweight or overweight patients only, extracted from the whole study population.

Discussion

When assessing a patient's renal function, it is recommended that raw GFR should be normalized with a patient's BSA because kidney size is dependent on body size [10].

The eClCr calculated by using the CG formula has been the most commonly applied method for determining drug dosing because most drug dosing recommendations available are based on pharmacokinetic studies using this formula, according to the 1998 United States Food and Drug Administration (FDA) guidance. The determination of eGFR by using the MDRD formula is very convenient because it is automatically reported in the laboratory results with the SCr levels. The National Kidney Disease Education Program (NKDEP) initially stated that the MDRD eGFR was only to be used for diagnosing and staging chronic kidney disease, but their updated recommendations in 2009 supported the use of MDRD eGFR for drug dosing. To support this recommendation, the NKDEP referenced the paper by Stevens et al. [11] comparing the MDRD and CG formulae [8, 9]. It is important to note that the BSA-adjusted MDRD eGFR values were converted by multiplying each individual's BSA and dividing it by 1.73 m², so that BSA normalization was reversed prior to the analysis. The NKDEP also emphasizes converting MDRD eGFR with BSA normalization to units of ml/min for determining drug dosing in very large and small patients.

In 2010, the FDA recommended that pharmaceutical manufacturers should provide drug dosing on the basis of both eClCr calculated by the CG formula and MDRD eGFR. Some have expressed concerns that using MDRD eGFR together with eClCr for drug dosing would be confusing, because the unit of MDRD eGFR (ml/min/1.73 m²) is not consistent with that of eClCr (ml/min) and the need to convert MDRD eGFR with BSA normalization to an individualized raw value (ml/min) may be overlooked.

Recent studies investigating the predictive value of the CV/eClCr or CV/eGFR ratios for CI-AKI suggested that maximally acceptable CV should be individually calculated by multiplying the cutoff value of the ratio and each patient's eGFR [1, 4–6]. The use of eGFR with BSA normalization can lead to an underestimation of the actual contrast removal rate in overweighted individuals and to an overestimation in underweighted ones [12], so the use of raw eGFR without BSA normalization rather than BSA-normalized eGFR is more appropriate when dealing with the toxicity of contrast medium. It is possible that patients with a higher BMI have higher actual or raw GFRs and are at a lower risk for the development of CI-AKI. Balemans et al. [13] reported that a low BMI was significantly associated with the development of CI-AKI. Clinicians need to be aware of the implication of individualized eGFR based on patient-specific BSA.

Cigarroa et al. [14] showed that a larger volume of contrast medium relative to BW is likely to contribute to the development of CI-AKI to determine the maximal acceptable contrast dose (MACD). The MACD is calculated by 5 ml of contrast $\times$ BW (kg) (maximum, 300 ml)/baseline SCr (mg/dl), an empiric equation that they had utilized over the past 10 years. Although the MACD has been validated in several studies, it is infrequently used in clinical practice because in a significant number of cases, CI-AKI can develop even if the MACD is not exceeded [15, 16]. The CV/raw MDRD eGFR ratio pharmacokinetically means the AUC representing the systemic exposure of the contrast agent, so it can be a better alternative.

So far, various studies have demonstrated that the CV/eClCr or CV/eGFR ratio is a significant risk factor for CI-AKI in patients undergoing PCI. Some included all patients with ischemic heart disease (IHD) while others included a selective group such as ST-segment elevation MI (STEMI). A recent article retrospectively analyzed patients with stable angina pectoris (AP), unstable AP (UAP), non-STEMI (NSTEMI) and STEMI [17]. The study population was divided by CV/eGFR ratio ranges of <2.0 , $2.0\text{--}2.9$, and ≥ 3.0 , based on the suggestion in the former study by Gurm et al. [18] that the restriction of CV to less than thrice and preferably twice of the eGFR might prevent CI-AKI. The study showed that a CV/eGFR ratio ≥ 3.0 was a significant risk factor of CI-AKI in the stable AP group, but not in the UAP, NSTEMI and STEMI groups. However, Gurm et al. [18] also retrospectively analyzed the whole patient group with all kinds of IHD undergoing PCI. Therefore, the suggestion by Gurm et al. [18] of minimizing CV may be generally acceptable for the patients with IHD for PCI, but it cannot be applied to relatively hemodynamically unstable patients. We may need another range of CV/eGFR ratios for using contrast media safely in patients with UAP and MI. In contrast, other prospective studies showed that the CV/eGFR ratio was a significant predictor for CI-AKI in the patients with STEMI [4, 6]. A large and prospective trial is required for the further confirmation that the CV/eGFR ratio is a significant variable in hemodynamically unstable patients such as those with MI.

Our study has some limitations. The cases in which an intra-aortic balloon pump was used due to severe hemodynamic instability could not be identified, so that some patients might develop AKI due to hemodynamic reasons, although CI-AKI is multifactorial, or a complex syndrome of AKI after the administration of contrast media.

In conclusion, our study showed that as a single risk value, the CV/raw MDRD eGFR ratio predicted CI-AKI better than the CV/BSA-normalized MDRD eGFR ratio; this strongly supports the idea that raw GFR without BSA normalization, in the unit of ml/min rather than ml/min/1.73 m², is considered when predicting CI-AKI.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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