

Safe Contrast Volumes for Preventing Contrast-Induced Nephropathy in Elderly Patients With Relatively Normal Renal Function During Percutaneous Coronary Intervention

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Abstract: The aim of this study was to evaluate contrast media volume to creatinine clearance (V/CrCl) ratio for predicting contrast-induced nephropathy (CIN) and to determine a safe V/CrCl cut off value to avoid CIN in elderly patients with relatively normal renal function during percutaneous coronary intervention (PCI).

We prospectively enrolled 1020 consecutive elderly patients (age ≥ 65 years) with relative normal renal function (baseline serum creatinine < 1.5 mg/dL) undergoing PCI. Receiver operating characteristic (ROC) curves were used to identify the optimal cut off value of V/CrCl for detecting CIN. The predictive value of V/CrCl for CIN was assessed with a multivariate logistic regression.

Thirty-nine patients (3.8%) developed CIN. There was a significant association between a higher V/CrCl ratio and CIN risk ($P < 0.001$). ROC curve analysis indicated that a V/CrCl ratio of 2.74 was a fair discriminator for CIN (C statistic = 0.68). After adjusting for other known CIN risk factors, V/CrCl ratios > 2.74 remained significantly associated with CIN (odds ratio = 3.21, 95% confidence interval [CI] 1.45–7.09, $P = 0.004$) and worse long-term mortality (hazard ratio = 1.96, 95% CI 1.14–3.38, $P = 0.016$).

A V/CrCl ratio > 2.74 was a significant independent predictor of CIN and was independently associated with long-term mortality in elderly patients with relatively normal renal function.

(*Medicine* 94(12):e615)

Abbreviations: CI = confidence interval, CIN = contrast-induced nephropathy, CKD = chronic kidney disease, CM = contrast media, MDRD = Modification of Diet in Renal Disease, OR = odds ratio, PCI = percutaneous coronary intervention, ROC = receiver operating characteristic, SCr = serum creatinine, STEMI = ST-segment elevation myocardial infarction, V/CrCl = CM volume to creatinine clearance.

INTRODUCTION

Contrast-induced nephropathy (CIN) is a common complication following percutaneous coronary intervention (PCI). CIN is associated with prolonged hospitalization, increased cardiovascular and renal morbidity, and all-cause mortality.¹ Decreased renal function and increased contrast media (CM) dose are both risk factors for CIN.² Because the CM volume is a modifiable factor, there have been several studies intended to find the safe volume of CM for risk reduction of CIN. A safe CM dose based on renal function has been proven to effectively prevent CIN. Recently, additional evidence has demonstrated that the CM volume to creatinine clearance (V/CrCl) ratio is an independent predictor of CIN following PCI in patients with decreased renal function^{3,4} and ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.^{5,6} For these high-risk patients, interventional cardiologists should pay close attention to intensive intravenous hydration, limiting CM volume, and serum creatinine (SCr) levels would be intensively monitored after PCI to detect CIN.

However, these measures are almost never typically administered to patients with normal baseline SCr (< 1.5 mg/dL), who are typically thought to have a low risk of CIN, although these patients constitute the majority of patients undergoing PCI. However, Lindsay et al⁷ and Chong et al⁸ observed that such patients were also at risk of developing CIN, with a corresponding increase in late adverse cardiac events and higher mortality. In addition to an elevated baseline SCr level, the presence of conditions such as a large CM volume may also contribute to renal injury. Therefore, evaluating a safe CM dose might also be useful for preventing CIN in such patients. However, few studies have investigated the safe CM volume in these patients. Thus, it is necessary to determine the safe

Editor: Ahmet Çağrı Aykan.

Received: October 15, 2014; revised: February 2, 2015; accepted: February 11, 2015.

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This study was supported by grants from the Science and Technology Planning Project of Guangdong Province (grant no. 2008A030201002), Guangdong Cardiovascular Institute; Guangdong Provincial Cardiovascular Clinical Medicine Research Fund (grant no. 2009X41); National Natural Science Foundation of China (grant no. 81270286). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript; the work was not funded by any industry sponsors.

The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000000615

amount of CM in patients with normal renal function for the prevention of CIN, especially for elderly patients. We investigated the predictive value of the V/CrCl ratio for CIN and long-term outcomes in these patients.

MATERIALS AND METHODS

Ethic Statements

This study protocol was approved by the ethics committee of the Guangdong General Hospital, and the study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before the procedure.

Study Population

We prospectively enrolled 1020 consecutive elderly patients (age ≥ 65 years) with baseline SCr < 1.5 mg/dL (132 mmol/dL) who were admitted to undergo PCI, between January 2010 and September 2012. The exclusion criteria were as follows: cardiogenic shock and pregnancy; CM allergy; use of CM within 7 days prior; severe heart valve diseases; treatment with nephroprotective drugs or nephrotoxic drugs; chronic peritoneal or hemodialytic treatment.

Biochemical Investigations and Assessment of Heart and Renal Function

SCr levels were measured upon admission (before PCI) and on day 1, 2, and 3 after CM exposure. Serum levels of fasting blood urea nitrogen, lipid profiles, glucose, albumin level, and other standard clinical parameters were measured during the morning of the day before the procedure. Left ventricular function was evaluated using echocardiography within 24 hours preoperatively. The CrCl was calculated by applying the Cockcroft–Gault formula to the SCr concentration, in which $\text{CrCl (mL/min)} = 140 \text{ years (age)} \times \text{weight (kg)} / 72 \times \text{SCr (mg/dL)}$ ($\times 0.85$ for female subjects). We evaluated the estimated glomerular filtration rate (eGFR) using the 4-variable Modification of Diet in Renal Disease (MDRD) equation based on Chinese patients: $175 \times \text{SCr (mg/dL)}^{-1.234} \times \text{age}^{-0.179}$ ($\times 0.79$ for women).

Percutaneous Coronary Intervention

PCI was performed by experienced interventional cardiologists using a standard technique. We used nonionic and low-osmolarity CM in patients (either Iopamiron, BRACCO, Guangzhou, China or Ultravist Bayer, Guangzhou, China, both 370 mg I/mL). The patients were hydrated with intravenous isotonic saline (0.9%) at a rate of 1 mL/kg body weight per hours for 1 to 8 hours before and 6 to 8 hours after PCI. In patients with left ventricular dysfunction (ejection fraction $< 40\%$) or overt heart failure, the hydration rate was reduced to 0.5 mL/kg/h. The use of aspirin, clopidogrel, β -adrenergic blocking agents, statins, angiotensin-converting enzyme inhibitors, and the indication to use an intra-aortic balloon pump (IABP) or inotropic drugs, was left to the discretion of the interventional cardiologists.

Clinical Follow-Up for End Points

Follow-up events were carefully monitored and recorded by trained nurses through office visits and telephone interviews for at least 3 years after PCI.

The primary study end-point was CIN, which was defined as an absolute increase in SCr of ≥ 0.5 mg/dL over baseline

values within 48 to 72 hours after CM exposure. The secondary end points included all-cause mortality, and major adverse clinical events (MACEs), including all-cause mortality, renal replacement therapy, nonfatal myocardial infarction, acute heart failure, and target vessel revascularization or cerebrovascular events during the observation period of hospitalization and follow-up.

Statistical Analysis

Demographics and traditional risk factors were compared among the V/CrCl quartiles and between patients with or without CIN. Continuous variables are described as their mean \pm standard deviation or as their median (interquartile range). Student *t* test or Wilcoxon rank sum test was performed to determine group differences. Categorical variables are reported as absolute values and percentages, and were analyzed using the χ^2 test or Fisher exact test. Analyses of the receiver operating characteristic (ROC) curves were performed to determine the cut off value of the V/CrCl, volume to MDRD equation (V/MDRD) ratio, and Mehran risk scores for predicting CIN. Risk factors were initially screened for univariate associations with CIN at $P < 0.20$, and the identified variables were assessed in a forward stepwise manner using a *P*-value criterion of ≤ 0.05 . The final model included the V/CrCl ratio and other baseline characteristics for which the results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Multivariate Cox regression analyses of mortality included baseline V/CrCl ratio (cut off values determined by ROC analysis) and other factors (age > 75 years, sex, anemia, diabetes mellitus [DM], hypertension, use of IABP, and left ventricular ejection fraction [LVEF] $< 40\%$). The cumulative mortality hazard or MACEs during follow-up for the baseline V/CrCl was analyzed using the Kaplan–Meier method, and the statistical assessments were performed using the log-rank test. All data analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). All probability values were 2-tailed, and the significance level was defined as $P < 0.05$.

RESULTS

Clinical and Laboratory Characteristics of the Patients

We included 1020 consecutive patients who underwent PCI and were eligible for the present study (mean age 72.5 ± 5.3 years, mean contrast volume 150.3 ± 58.7 mL, mean Mehran risk score 5.8 ± 3.8). Based on the V/CrCl, the quartiles of the V/CrCl ratio for all patients were as follows: quartile (Q1) (< 1.76 , $n = 255$), Q2 (1.76 – 2.48 , $n = 255$), Q3 (2.48 – 3.31 , $n = 255$), and Q4 (> 3.31 , $n = 255$). From quartile Q1 to Q4, there was a positive trend with older age, the preprocedural SCr level, CM dose, number of diseased vessels, ratio of V/CrCl or V/MDRD, and Mehran risk score. There was a negative trend with the preprocedural renal function (evaluated by the CrCl or MDRD). However, there were no significant differences in the incidence of hypertension, DM, dyslipidemia, or anemia among the different quartiles of the V/CrCl ratio, or in the use of medication during hospital stay (Table 1).

Overall, CIN was observed in 39 patients (3.8%). The patients with CIN were older and had lower levels of LVEF and preprocedural renal function than the patients without CIN. A higher ratio of V/CrCl or V/MDRD, and higher CIN Mehran risk scores were more prevalent in the patients with CIN. However, the prevalence of smoking, hypertension, DM,

TABLE 1. Baseline Characteristics of the V/ CrCl Ratio Quartiles

Variables	V/CrCl Quartiles				P Value
	Q1 (n = 255)	Q2 (n = 255)	Q3 (n = 255)	Q4 (n = 255)	
Demographics					
Age, y	70.60 ± 4.45	72.33 ± 5.22	72.49 ± 5.27	74.44 ± 5.37	<0.001
Age >75 y, n (%)	39 (15.3%)	72 (28.2%)	70 (27.5%)	107 (42.0%)	<0.001
Female, n (%)	82 (32.2%)	74 (29.0%)	82 (32.2%)	80 (31.4%)	0.853
Systolic BP, mm Hg	133.06 ± 21.03	133.99 ± 19.79	130.41 ± 20.65	134.12 ± 22.59	0.163
Diastolic BP, mm Hg	74.67 ± 10.71	74.36 ± 10.99	73.70 ± 11.27	74.16 ± 11.28	0.792
Medical history, n (%)					
DM	64 (25.1%)	79 (31.0%)	69 (27.1%)	64 (25.1%)	0.395
Smoker	69 (27.1%)	83 (32.5%)	85 (33.3%)	77 (30.2%)	0.415
Hypertension	153 (60.0%)	154 (60.4%)	176 (69.0%)	174 (68.2%)	0.047
Prior MI	22 (8.6%)	20 (7.8%)	23 (9.0%)	36 (14.1%)	0.073
Prior CABG	1 (0.4%)	2 (0.8%)	3 (1.2%)	3 (1.2%)	0.745
Laboratory findings					
Preprocedural SCr, µmol/L	73.98 ± 16.46	84.29 ± 17.87	88.44 ± 17.24	98.82 ± 18.40	<0.001
Preprocedural CrCl, mL/min	75.04 ± 19.08	61.34 ± 14.12	56.12 ± 13.58	46.81 ± 11.83	<0.001
MDRD, mL/min/1.73 m ²	92.59 ± 21.12	80.24 ± 18.39	75.14 ± 17.06	66.67 ± 16.28	<0.001
HbA1c, %	6.52 ± 1.26	6.56 ± 1.30	6.58 ± 1.32	6.60 ± 2.17	0.958
HCT	0.38 ± 0.04	0.38 ± 0.04	0.37 ± 0.05	0.37 ± 0.04	0.006
Anemia, n (%)	96 (37.6%)	102 (40.0%)	119 (46.7%)	110 (43.1%)	0.18
Serum albumin, g/L	35.02 ± 4.37	34.26 ± 4.12	33.71 ± 4.10	33.85 ± 3.96	0.002
Uric acid, µmol/L	347.16 ± 94.47	361.06 ± 106.46	363.11 ± 103.91	381.11 ± 109.12	0.012
LVEF, %	60.27 ± 12.26	59.08 ± 11.71	57.93 ± 11.76	57.51 ± 11.02	0.049
LVEF <40%, n (%)	20(8.7)	19 (8.4)	19 (8.4)	17 (7.1)	0.924
Medication during hospital stay, n (%)					
ACEI/ARB	234 (91.8%)	229 (89.8%)	226 (88.6%)	238 (93.3%)	0.260
β-Blocker	224(87.8)	212 (83.1)	209 (82.0)	220 (86.3)	0.221
Calcium channel blocker	57 (22.4%)	55 (21.6%)	48 (18.8%)	65 (25.5%)	0.341
Statin	252 (98.8%)	247 (96.9%)	249 (97.6%)	252 (98.8%)	0.299
Procedural characteristic					
Contrast volume, mL	98.22 ± 23.77	130.49 ± 32.56	160.80 ± 38.79	211.51 ± 60.98	<0.001
Contrast exposure time, min	68.36 ± 34.04	73.67 ± 34.53	84.70 ± 40.20	107.84 ± 45.12	<0.001
Number of diseased vessels, n	2.18 ± 0.90	2.15 ± 0.93	2.50 ± 0.85	2.65 ± 0.87	<0.001
Total length of stent, mm	37.27 ± 23.61	42.09 ± 26.38	54.57 ± 31.79	58.47 ± 33.78	<0.001
Mehran risk score	4.30 ± 3.20	5.60 ± 3.57	6.07 ± 3.81	7.24 ± 4.08	<0.001
V/CrCl	1.35 ± 0.30	2.13 ± 0.21	2.87 ± 0.24	4.64 ± 1.28	<0.001
V/MDRD	1.09 ± 0.28	1.66 ± 0.35	2.18 ± 0.43	3.28 ± 0.98	<0.001

Mehran risk score is the model to define CIN by Mehran et al.⁹ Anemia was defined using World Health Organization criteria; baseline hematocrit value <39% for men and <36% for women. ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, BP = blood pressure, CABG = coronary artery bypass grafting, CIN = contrast-induced nephropathy, CM = contrast media, CrCl = creatinine clearance, DM = diabetes mellitus, HbA1c = hemoglobin A1c, LVEF = left ventricular ejection fraction, MDRD = Modification of Diet in Renal Disease, MI = myocardial infarction, SCr = serum creatinine, V/CrCl = CM volume to creatinine clearance, V/MDRD = volume to MDRD equation.

history of previous myocardial infarction, previous coronary artery bypass grafting, and anemia were not significantly different between the groups (Table 2).

Impact of V/CrCl and CIN on In-Hospital Outcomes

The patients with a high V/CrCl ratio were more likely to develop CIN, including 5 patients (1.96%) in Q1, 6 (2.35%) in Q2, 6 (2.35%) in Q3, and 22 (8.63%) in Q4 (P < 0.001) (Figure 1A). The patients with an increasing V/CrCl ratio experienced a higher rate of IABP (P = 0.001). However, the incidence of in-hospital death, stroke, acute heart failure, and

the need for renal replacement were not significantly different among the different V/CrCl ratio quartiles.

Compared with the patients without CIN, the patients with CIN showed a significantly higher rate of in-hospital mortality (23.1% vs. 0.7%, P < 0.001), a significantly higher rate of other in-hospital complications, such as requirement for IABP (35.9% vs. 2.0%, P < 0.001), and the need for renal replacement (10.3% vs. 0.3%, P < 0.001) (Figure 1B.)

Predictors of CIN

ROC curve analysis demonstrated that the area under the curve (AUC) for the V/CrCl ratio was 0.680 for CIN. For the

TABLE 2. Baseline Clinical Features in Patients With and Without CIN

Variables	CIN		P Value
	No (n = 981)	Yes (n = 39)	
Demographics			
Age, y	72.33 ± 5.16	75.97 ± 6.62	0.002
Age >75 y, (%)	716 (73.0%)	16 (41.0%)	<0.001
Females, %	303 (30.9%)	15 (38.5%)	0.317
Systolic BP, mm Hg	132.99 ± 20.69	130.54 ± 29.09	0.605
Diastolic BP, mm Hg	74.28 ± 10.93	72.74 ± 13.78	0.494
Medical history, n (%)			
Smokers	303 (30.9%)	11 (28.2%)	0.722
Hypertension	629 (64.1%)	28 (71.8%)	0.326
DM	264 (26.9%)	12 (30.8%)	0.595
Prior MI	97 (9.9%)	4 (10.3%)	0.940
Prior CABG	9 (0.9%)	0 (0.0%)	0.548
Laboratory findings			
Preprocedural SCr, $\mu\text{mol/L}$	85.85 ± 19.28	99.77 ± 23.27	<0.001
Preprocedural CrCl, mL/min	60.35 ± 17.84	46.59 ± 18.22	<0.001
MDRD, mL/min/1.73 m ²	79.15 ± 20.30	66.39 ± 23.18	<0.001
LVEF, %	58.98 ± 11.48	52.21 ± 14.96	0.008
LVEF <40%	68 (7.7)	7 (17.9)	0.022
HCT, %	0.38 ± 0.04	0.36 ± 0.06	0.112
Anemia, n (%)	410 (41.8%)	17 (43.6%)	0.824
Serum albumin, g/L	34.34 ± 4.11	31.15 ± 4.45	<0.001
Uric acid, $\mu\text{mol/L}$	360.72 ± 102.84	418.07 ± 120.87	0.003
Medication, n (%)			
ACEI/ARB	892 (90.9%)	35 (89.7%)	0.801
β -Blocker	839 (85.5)	26 (66.7)	0.001
Calcium channel blocker	217 (22.1%)	8 (20.5%)	0.812
Statins	963 (98.2%)	37 (94.9%)	0.146
Procedural characteristic			
Contrast volume, mL	150.10 ± 58.71	154.23 ± 59.92	0.667
Contrast exposure time, min	83.23 ± 41.57	94.29 ± 40.22	0.108
Number of diseased vessels, n	2.36 ± 0.90	2.62 ± 1.09	0.083
V/CrCl	2.70 ± 1.35	3.84 ± 2.05	0.001
V/MDRD	2.03 ± 0.97	2.60 ± 1.25	0.007
Mehran risk score	5.65 ± 3.70	9.56 ± 4.88	<0.001

Mehran risk score is the model to define CIN by Mehran et al.⁹ Anemia was defined using World Health Organization criteria; baseline hematocrit value <39% for men and <36% for women. ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, BP = blood pressure, CABG = coronary artery bypass grafting, CIN = contrast-induced nephropathy, CM = contrast media, CrCl = creatinine clearance, DM = diabetes mellitus, HCT = hematocrit, LVEF = left ventricular ejection fraction, MDRD = Modification of Diet in Renal Disease, MI = myocardial infarction, SCr = serum creatinine, V/CrCl = CM volume to creatinine clearance, V/MDRD = volume to MDRD equation.

Mehran risk score, the AUC was similar to the V/CrCl ratio for CIN (0.735, $P=0.204$). The Youden index demonstrated that the optimal cut off level for the V/CrCl ratio was >2.74, which exhibited 76.2% sensitivity and 70.6% specificity for predicting CIN. Although there was no significant difference between the V/CrCl and the V/MDRD, the AUC of the V/MDRD (0.648) was lower than the V/CrCl (Figure 2).

According to the univariate logistic regression analysis, a V/CrCl ratio >2.74 was a significant predictor of CIN (OR = 3.78, 95% CI 1.86–7.67, $P<0.001$). In the multivariate analysis, a V/CrCl ratio of >2.74 (OR = 3.21, 95% CI 1.45–7.09, $P=0.004$) remained an independent risk factor of CIN after adjusting for other potential risk factors. In addition, when we included the Mehran risk score (increment 1 point) to the multivariate model instead of the individual variables (age >75 years, anemia, DM, and IABP) that are incorporated in it,

we also demonstrated that V/CrCl ratio >2.74 was an independent risk factor for CIN (OR = 2.84, 95% CI 1.34–6.03, $P=0.007$). Age >75 years, LVEF <40%, the requirement for IABP, and Mehran risk scores (increment 1 point) were other independent predictors of CIN (OR = 2.69, 95% CI 1.29–5.61, $P=0.009$; OR = 2.94, 95% CI 1.12–7.68, $P=0.028$; OR = 1.21, 95% CI 1.12–1.31, $P=0.007$; OR = 17.94, 95% CI 7.07–41.77, $P<0.001$). However, we did not find multi-vessel disease to be an independent risk factor of CIN in our patients (OR = 0.51, 95% CI 0.21–1.21, $P=0.128$) (Table 3).

Impact of V/CrCl and CIN on Follow-Up Outcomes

The median follow-up period was 2.51 ± 0.86 years (interquartile range 1.80–3.27 years), and data were available for all

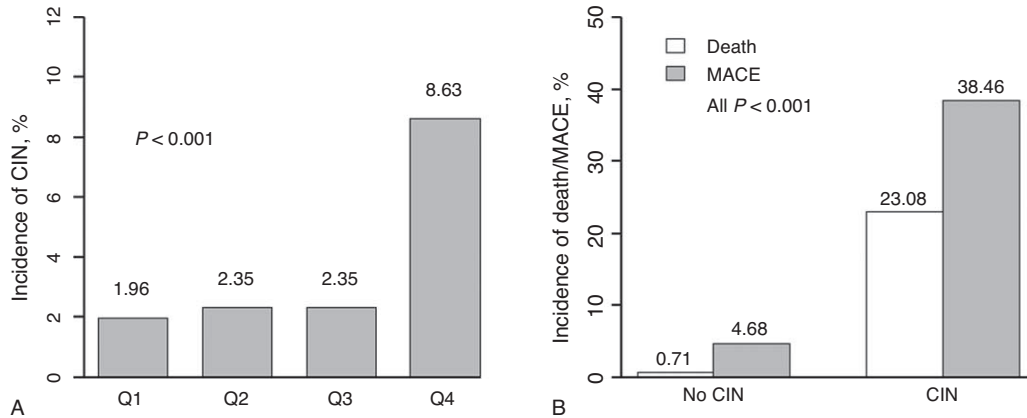


FIGURE 1. (A) Relationship between the contrast volume to creatinine clearance ratio and the percentage of patients with CIN after cardiac catheterization (*P* < 0.001, overall and for the trend). (B) Relationship between CIN and in-hospital death or MACEs (all *P* < 0.001). CIN = contrast-induced nephropathy, MACE = major adverse clinical event.

who survived to discharge. According to the log-rank analysis, the patients with a V/CrCl ratio >2.74 presented with a higher rate of all-cause mortality than the patients with a V/CrCl ratio ≤2.74 (*P* = 0.002). The patients with a V/CrCl ratio >2.74 also experienced a relative higher rate of MACEs than the patients with a V/CrCl ratio ≤2.74, although this was not a statistically significant difference (*P* = 0.065) (Figure 3). In addition, the patients developing CIN presented with a higher rate of all-cause mortality or MACEs than those without CIN during follow-up (both *P* < 0.001) (Figure 4). Furthermore, Cox regression analysis indicated that the V/CrCl ratio >2.74 remained a significant risk factor for death after PCI, even after adjusting for the baseline clinical variables (hazard ratio = 1.96, 95% CI 1.14–3.38, *P* = 0.016) (Figure 5).

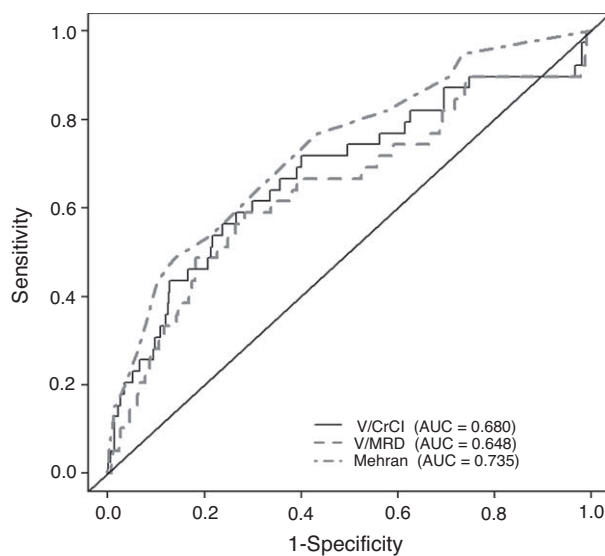


FIGURE 2. ROC curve for the prediction of CIN using the V/CrCl, V/MRD, and Mehran risk score. AUC = area under the curve, CIN = contrast-induced nephropathy, CM = contrast media, ROC = receiver operating characteristic, V/CrCl = CM volume to creatinine clearance, V/MRD = volume to Modification of Diet in Renal Disease equation.

DISCUSSION

The present study was performed to evaluate the safe CM dose for CIN in elderly patients with relatively normal renal function, and we demonstrated that the V/CrCl ratio was independently associated with CIN and poor long-term outcomes. Additionally, the V/MDRD ratio showed a similar predictive value for CIN to that of the V/CrCl. Furthermore, a V/CrCl ratio >2.74 demonstrated a good predictive value for CIN and long-term patient outcomes.

The diagnosis of CIN was also used for patients developing acute kidney injury secondary to intravascular CM exposure. CIN occurs in both ambulatory and hospitalized patients, and the immediate and long-term prognoses of these problems are similar to those of other causes of acute kidney injury. In clinical practice, patients with elevated baseline SCr should receive sufficient perioperative CIN prophylaxis, and the safe CM dose should be calculated based upon renal function before the procedure according to recent guidelines from the American College of Cardiology¹⁰ and the European Society of Cardiology.¹¹ However, these guidelines do not recommend that patients with normal SCr values receive any prophylaxis, nor should doctors need to limit the CM dose, as such patients are typically thought to have a low risk of CIN. However, previous studies have demonstrated that even in patients with normal SCr, CIN can develop and lead to complicated clinical outcomes similar to those of patients with chronic renal insufficiency.^{7,8} Wacker-Gußmann et al used the same definition for secondary endpoints as our present study, and they found that the incidence of CIN was 3.7% in patients with SCr levels in the upper normal range, which is in agreement with our results (3.8%).¹² In addition, Raposeiras-Roubin et al¹³ recently demonstrated that an increase in ≥0.5 mg/dL was an independent predictor of in-hospital cardiac events in patients with normal renal function. In the present study, we also found that patients who developed CIN had poor in-hospital and long-term outcomes in such patients. Therefore, these patients should also receive prophylaxis measures.

A large CM volume is a key contributor to CIN in patients with normal renal function,^{7,8} and a reduction in CM volume has been reported to be a possible means for preventing CIN.¹⁴ Therefore, determining the safe CM volume is important for preventing CIN. Several cut off thresholds for safe CM volume have been reported. However, the V/CrCl ratio is correlated

TABLE 3. Univariate Analysis and Multivariate Associations Between CIN and V/CrCl

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Model 1						
V/CrCl >2.74	3.78	1.86–7.67	<0.001	3.21	1.45–7.09	0.004
Age >75 y	3.88	2.02–7.47	<0.001	2.69	1.29–5.61	0.009
Hypertension	1.42	0.70–2.90	0.329	1.08	0.49–2.36	0.849
Diabetes	1.21	0.60–2.42	0.595	1.20	0.55–2.61	0.650
Anemia	1.08	0.56–2.05	0.824	0.99	0.48–2.06	0.983
LVEF <40%	2.61	1.11–6.15	0.027	2.94	1.12–7.68	0.028
Multivessel disease	0.84	0.39–1.80	0.660	0.51	0.21–1.21	0.128
IABP	26.91	12.21–59.29	<0.001	17.94	7.70–41.77	<0.001
Model 2						
V/CrCl >2.74				2.84	1.34–6.03	0.007
Mehran risk score	1.24	1.16–1.34	<0.001	1.21	1.12–1.31	<0.001
Hypertension				1.34	0.63–2.85	0.442
Multivessel disease				0.52	0.23–1.17	0.112
LVEF <40%				2.81	1.11–7.12	0.029

Mehran risk score is the model to define CIN by Mehran et al.⁹ Anemia was defined using World Health Organization criteria; baseline hematocrit value <39% for men and <36% for women. CI = confidence interval, CIN = contrast-induced nephropathy, CM = contrast media, IABP = intra-aortic balloon pump, LVEF = left ventricular ejection fraction, OR = odds ratio, V/CrCl = CM volume to creatinine clearance.

with the AUC of the CM concentration over time, and it best represents the CM dose and renal function. Therefore, this index should more closely predict the safety profile of CM than the absolute CM volume alone, particularly with respect to the risk of CIN.¹⁵ Indeed, the V/CrCl ratio, an easy and clinically feasible method for determining the maximum safe CM volume, has been reported to be a predictor of CIN following PCI.

Laskey et al³ observed that a V/CrCl ratio >3.7 demonstrated the optimal sensitivity and specificity for detecting CIN, and it remained an independent predictor for CIN after adjusting for other factors. However, these authors mostly studied the

effects of CM according to the SCr levels during the first 24 hours (rather than 48–72 hours), and only 6.8% of had 24- and 48-hours SCr measurements in their study, thereby underestimating the incidence of CIN. In addition, this previous study could neither ascribe causality nor describe the relationship between CM and clinical end points (eg, death). Our present study with 48 to 72 hours sampling of SCr after the procedure demonstrated that the V/CrCl ratio was associated with CIN and long-term outcomes, and that the predictive potential of the V/CrCl ratio was independent of other known clinical and laboratory-based risk factors of CIN. Recently, Capodanno et al studied 722 patients undergoing cardiac

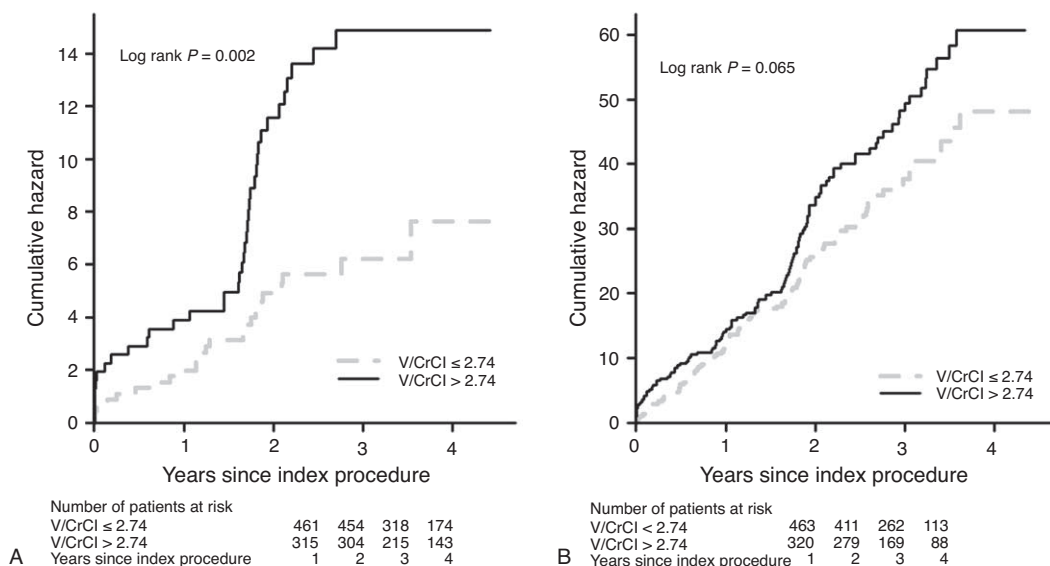


FIGURE 3. Cumulative mortality (A) or MACEs (B) as a function of time for patients with a V/CrCl ratio >2.74 or ≤2.74. CM = contrast media, MACE = major adverse clinical event, V/CrCl = CM volume to creatinine clearance.

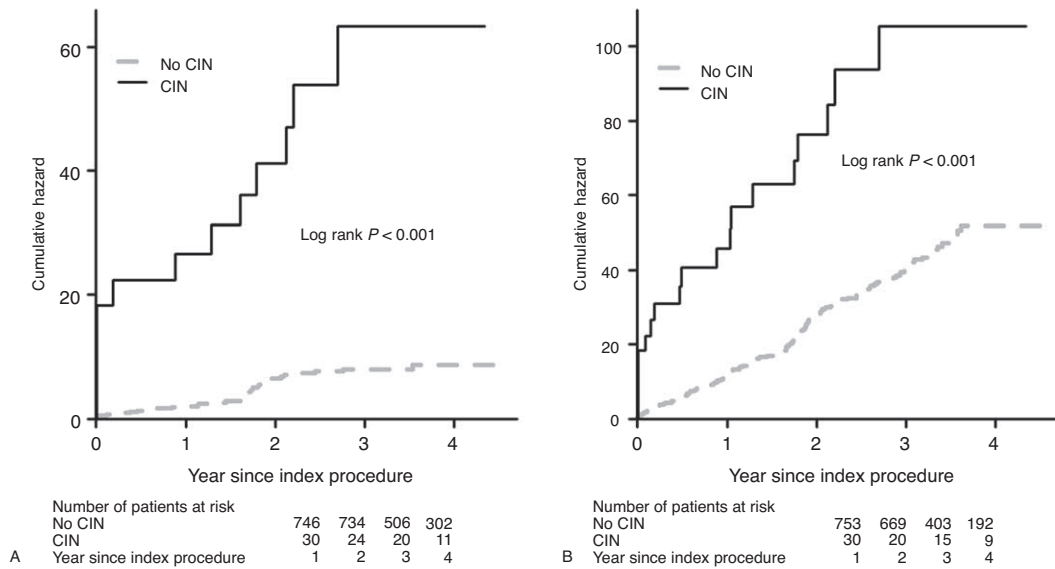


FIGURE 4. Cumulative mortality (A) or MACEs (B) as a function of time for patients with CIN or without CIN. CIN = contrast-induced nephropathy, MACE = major adverse clinical event.

catheterization and demonstrated that a V/CrCl >4 significantly predicted the risk of an early postprocedural rise in SCr.¹⁶ A similar result was found in the recent study performed by Capodanno et al,¹⁶ in which these authors confirmed the predictive value of V/CrCl >4 for CIN regardless of the CIN definition adopted. However, assuming a low incidence of CIN in elderly patients with relatively normal SCr, most previous studies evaluating the safe CM dose for the prevention of CIN have included patients with moderate and severe increases in SCr or patients at high risk of CIN, such as patients with chronic kidney disease (CKD), STEMI, or DM. In recent studies, there are different conclusions about the ratio of V/CrCl. Ogata et al⁴ included CKD patients with an eGFR <30 mL/min/1.73 m² undergoing elective PCI, and they found that an extreme reduction of CV to CV/eGFR ratio <1.0 may reduce CIN and achieve better clinical outcomes following PCI in such

patients. Mager et al¹⁷ observed that a V/GFR >3.7 was a strong independent predictor of CIN in patients with STEMI undergoing primary PCI. Worasuwannarak and Pornratanarangsri¹⁸ reported that the cut off value for the V/CrCl ratio was ≥2.60 in patients with DM undergoing elective PCI. Recently, we performed a study of patients with a reduced ejection fraction (<40%), and we demonstrated that a V/CrCl ratio <3.87 might be valuable in predicting the risk of CIN in such patients undergoing PCI.¹⁹ However, the present study demonstrated the optimal cut off value for the V/CrCl ratio (2.74) in elderly patients with relatively normal renal function undergoing PCI. The difference in cut off values for the V/CrCl ratio and the incidence of CIN reported in these previous studies can be explained by the use of different definitions of CIN (48–72 hours or 24 hours) and the different percentages of patients with CKD, STEMI, and DM. In addition, we also demonstrated that

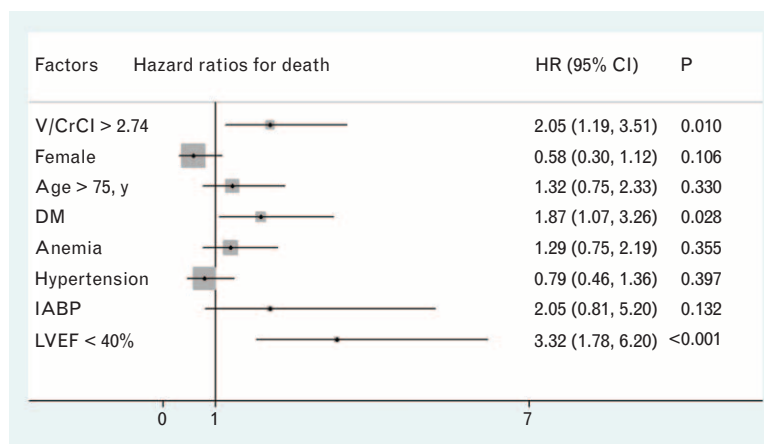


FIGURE 5. Multivariate Cox regression analysis indicates that a V/CrCl ratio >2.74 is significantly associated with an increased risk of death within 3 years follow-up after PCI. CI = confidence interval, CM = contrast media, DM = diabetes mellitus, HR = hazard ratio, IABP = intra-aortic balloon pump, LVEF = left ventricular ejection fraction, PCI = percutaneous coronary intervention, V/CrCl = CM volume to creatinine clearance.

the Mehran score was strongly associated with CIN development. The Mehran risk score is the most widely used and classic model for CIN, and it has 8 clinical and procedural factors, including age >75 years, CM volume, and the presence of chronic heart failure, hypotension, anemia, DM, and CKD. The Mehran score was used for CIN evaluation only after CM exposure.⁹ However, the optimal cut off value for the V/CrCl ratio plays an important role in calculating the safe CM dose for preventing CIN before the procedure. Furthermore, the predictive value of the Mehran risk score was similar to that of the present V/CrCl ratio.

Although the pathophysiology of CIN is complex and remains unclear, researchers generally considered that direct cytotoxic effects, regional hypoxia, and renal haemodynamics play important roles in developing CIN.²⁰ The direct toxicity by CM can lead to apoptosis and cell death of both endothelial and tubular cells, and could be related to harmful effects of free radicals and oxidative stress, resulting in the development of CIN.²¹ In addition, previous studies have demonstrated that CM in the medulla can decrease oxygen delivery and increase oxygen consumption, leading to the renal medullary hypoxia. Moreover, this was related to either a decrease in vasodilators (nitric oxide or prostaglandins) or an increase in vasoconstrictors (adenosine and endothelin). Increased intratubular pressure secondary to CM-induced diuresis, increased urinary viscosity, and tubular obstruction were also involved in developing CIN.²²

In addition, previous studies have demonstrated that patients with multivessel coronary diseases often suffer complications including longer procedural durations, greater CM use, lower LVEF, and more frequent periprocedural hemodynamic instability^{23,24} which play important roles in CIN development. Therefore, some researchers have argued that a multivessel coronary disease is an independent risk factor of CIN.¹⁷ Additionally, some studies have indicated that The synergy between PCI with Taxus and cardiac surgery score, which has been developed to assess the severity and complexity of coronary artery disease to determine the appropriate revascularization strategy, is an independent predictor of CIN in patients with ST elevation myocardial infarction treated with primary PCI.^{25,26} However, Kurtul et al²⁶ did not demonstrate that multivessel disease was strongly associated with CIN after adjusting for some potential risk factors in patients with acute coronary syndrome, which is in accordance with our present result. The differences among these studies might be related to the different patient populations included.

Furthermore, few studies have evaluated the predictive value of the V/MDRD ratio for CIN. Nozue et al²⁷ retrospectively investigated the value of the V/MDRD ratio for CIN and reported that the V/MDRD ratio was a significant independent predictor of CIN, and our result confirmed these findings. The present prospective study further assessed the predictive value of the V/CrCl ratio for prognostic outcomes (ie, the 2-year death rate) in elderly patients with relatively normal renal function. In particular, we found that patients with a V/CrCl ratio >2.74 experienced more complications such as a higher incidence of MACEs and showed increased follow-up mortality.

Clinical Implications

The findings of the present study may be clinically important because elderly patients with relatively normal renal function usually do not receive prophylaxis (eg, hydration and calculation of the safe CM dose) or undergo routine follow-ups including laboratory control of renal parameters after CM exposure. The present data support the use of V/CrCl as a

practical index to determine the safe or maximum amount of CM allowed for each procedure. In this patient population, it is possible to minimize the CM volume by making adjustments, and intensive hydration would be recommended before and after PCI for the prevention of CIN. After procedure, cardiologists should also calculate the V/CrCl ratio to identify patients at high risk for CIN, such that intensive renal function monitoring and timely prophylactic measures can be performed. Lastly, the predictive value of the V/CrCl ratio for CIN was similar to that of the Mehran risk score.

Limitations

The present study had several limitations. First, because this prospective, observational study was conducted in a single center, the evidence may not be as compelling as that obtained in a randomized controlled trial. Second, variation in the measurement times may have led to overlooked peak levels of SCr after procedure, which may have also led to an underestimation of the true incidence of nephropathy in the current study population. Finally, the predictive value of the V/CrCl ratio for CIN and long-term outcomes was demonstrated in elderly patients with relatively normal renal function undergoing PCI. Therefore, it is not known whether the present cut off value could be applied to other patient groups.

CONCLUSION

We demonstrated that a V/CrCl ratio >2.74 was an independent predictor of CIN and that an extreme reduction in the CM to a V/CrCl ratio <2.74 may reduce CIN and achieve better clinical outcomes following PCI in elderly patients with relatively normal renal function.

REFERENCES

1. Tsai TT, Patel UD, Chang TI, et al. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR cath-PCI registry. *JACC Cardiovasc Interv*. 2014;7:1–9.
2. Aurelio A, Durante A. Contrast-induced nephropathy in percutaneous coronary interventions: pathogenesis, risk factors, outcome, prevention and treatment. *Cardiology*. 2014;128:62–72.
3. Laskey WK, Jenkins C, Selzer F, et al. A pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention. *J Am Coll Cardiol*. 2007;50:584–590.
4. Ogata N, Ikari Y, Nanasato M, et al. Safety margin of minimized contrast volume during percutaneous coronary intervention in patients with chronic kidney disease. *Cardiovasc Interv Ther*. 2014;29:209–215.
5. Liu Y, Tan N, Zhou YL, et al. The contrast medium volume to estimated glomerular filtration rate ratio as a predictor of contrast-induced nephropathy after primary percutaneous coronary intervention. *Int Urol Nephrol*. 2012;44:221–229.
6. Ando G, de Gregorio C, Morabito G, et al. Renal function-adjusted contrast volume redefines the baseline estimation of contrast-induced acute kidney injury risk in patients undergoing primary percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2014;7:465–472.
7. Chong E, Poh KK, Liang S, et al. Risk factors and clinical outcomes for contrast-induced nephropathy after percutaneous coronary intervention in patients with normal serum creatinine. *Ann Acad Med Singapore*. 2010;39:374–380.
8. Lindsay J, Apple S, Pinnow EE, et al. Percutaneous coronary intervention-associated nephropathy foreshadows increased risk of

- late adverse events in patients with normal baseline serum creatinine. *Catheter Cardiovasc Interv.* 2003;59:338–343.
9. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol.* 2004;44:1393–1399.
 10. Anderson JL, Adams CD, Antman EM, et al. 2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2011;123:e426–e579.
 11. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35:2541–2619.
 12. Wacker-Gußmann A, Bühren K, Schultheiss C, et al. Prediction of contrast-induced nephropathy in patients with serum creatinine levels in the upper normal range by cystatin C: a prospective study in 374 patients. *Am J Roentgenol.* 2014;202:452–458.
 13. Raposeiras-Roubin S, Aguiar-Souto P, Barreiro-Pardal C, et al. GRACE risk score predicts contrast-induced nephropathy in patients with acute coronary syndrome and normal renal function. *Angiology.* 2013;64:31–39.
 14. Kane GC, Doyle BJ, Lerman A, et al. Ultra-low contrast volumes reduce rates of contrast-induced nephropathy in patients with chronic kidney disease undergoing coronary angiography. *J Am Coll Cardiol.* 2008;51:89–90.
 15. Dangas G, Iakovou I, Nikolsky E, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol.* 2005;95:13–19.
 16. Capodanno D, Ministeri M, Cumbo S, et al. Volume-to-creatinine clearance ratio in patients undergoing coronary angiography with or without percutaneous coronary intervention: implications of varying definitions of contrast-induced nephropathy. *Catheter Cardiovasc Interv.* 2014;83:907–912.
 17. Mager A, Vaknin AH, Lev EI, et al. The ratio of contrast volume to glomerular filtration rate predicts outcomes after percutaneous coronary intervention for ST-segment elevation acute myocardial infarction. *Catheter Cardiovasc Interv.* 2011;78:198–201.
 18. Worasuwannarak S, Pornratanarangsri S. Prediction of contrast-induced nephropathy in diabetic patients undergoing elective cardiac catheterization or PCI: role of volume-to-creatinine clearance ratio and iodine dose-to-creatinine clearance ratio. *J Med Assoc Thai.* 2010;93(Suppl 1):S29–S34.
 19. Liu Y, Chen SQ, Duan CY, et al. Contrast volume-to-creatinine clearance ratio predicts the risk of contrast-induced nephropathy after percutaneous coronary intervention in patients with reduced ejection fraction. *Angiology.*
 20. Seeliger E, Sendeski M, Rihal CS, et al. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. *Eur Heart J.* 2012;33:2007–2015.
 21. Andreucci M, Faga T, Pisani A, et al. Acute kidney injury by radiographic contrast media: pathogenesis and prevention. *BioMed Res Int.* 2014;2014:1–20.
 22. Andreucci M, Solomon R, Tasanarong A. Side effects of radiographic contrast media: pathogenesis, risk factors, and prevention. *BioMed Res Int.* 2014;2014:1–20.
 23. Cicek G, Bozbay M, Acikgoz SK, et al. The ratio of contrast volume to glomerular filtration rate predicts in-hospital and six months mortality in patients undergoing primary angioplasty for ST-elevation myocardial infarction. *Cardiol J.* 2015;22:101–107.
 24. Aykan AÇ, Gül İ, Gökdeniz T, et al. Is coronary artery disease complexity valuable in the prediction of contrast induced nephropathy besides Mehran risk score, in patients with ST elevation myocardial infarction treated with primary percutaneous coronary intervention? *Heart Lung Circ.* 2013;22:836–843.
 25. Oduncu V, Erkol A, Karabay CY, et al. Relation of the severity of contrast induced nephropathy to SYNTAX score and long term prognosis in patients treated with primary percutaneous coronary intervention. *Int J Cardiol.* 2013;168:3480–3485.
 26. Kurtul A, Duran M, Yarlioglu M, et al. Association between N-terminal pro-brain natriuretic peptide levels and contrast-induced nephropathy in patients undergoing percutaneous coronary intervention for acute coronary syndrome. *Clin Cardiol.* 2014;37:485–492.
 27. Nozue T, Michishita I, Iwaki T, et al. Contrast medium volume to estimated glomerular filtration rate ratio as a predictor of contrast-induced nephropathy developing after elective percutaneous coronary intervention. *J Cardiol.* 2009;54:214–220.