ORIGINAL RESEARCH

Persistent Renal Dysfunction in Patients Undergoing Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction

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***Background*—**The long-term prognosis of patients with acute myocardial infarction who develop persistent renal dysfunction (RD) remains unclear. We investigated risk factors and prognostic implications of persistent RD after contrast-induced nephropathy (CIN) in patients with acute myocardial infarction after primary percutaneous coronary intervention.

***Methods and Results*—**We enrolled 952 consecutive patients who underwent primary percutaneous coronary intervention for acute myocardial infarction. CIN was defined as an increase in serum creatinine levels ≥0.5 mg/dL or ≥25% from baseline within 72 hours after percutaneous coronary intervention. Persistent RD was defined as residual impairment of renal function over 2 weeks, and transient RD was defined as recovery of renal function within 2 weeks, after CIN. The overall incidence of CIN was 8.8% and that of persistent CIN was 3.1%. A receiver-operator characteristic curve showed that the optimal cutoff value of the contrast volume/baseline estimated glomerular filtration rate ratio for persistent CIN was 3.45. In multivariable logistic analysis, a contrast volume/baseline estimated glomerular filtration rate >3.45 was an independent correlate of persistent RD. At 3 years, the incidence of death was significantly higher in patients with persistent RD than in those with transient RD (P=0.001) and in those without CIN (P<0.001). Cox regression analysis showed that persistent RD (hazard ratio, 4.99; 95% CI, 2.30–10.8; P<0.001) was a significant risk factor for mortality. A similar trend was observed for the combined end points, which included mortality, hemodialysis, stroke, and acute myocardial infarction.

***Conclusions*—**Persistent RD, but not transient RD, is independently associated with long-term mortality. A contrast volume/baseline estimated glomerular filtration rate >3.45 is an independent predictor of persistent RD. **(*J Am Heart Assoc*. 2019;8: e014096. DOI: 10.1161/JAHA.119.014096.)**

Key Words: acute myocardial infarction • contrast-induced nephropathy • percutaneous coronary intervention

Contrast-induced nephropathy (CIN) is a relatively common complication of percutaneous coronary intervention (PCI). Recent studies have shown that CIN is associated with increased in-hospital and long-term morbidity and mortality.[1,2]

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The risk for CIN is significantly higher in patients with acute myocardial infarction (AMI) after primary PCI than in those with stable coronary heart disease after staged PCI, and CIN predicts poorer clinical outcomes in the population with AMI.[2,3]

In most patients who develop CIN, renal dysfunction (RD) is often transient and reversible.[4] However, some cases of CIN develop a persistent elevation in creatinine levels, resulting in increased short- and long-term morbidity and mortality.[4,5] However, the prognostic implications of persistent RD after CIN in patients with AMI who undergo primary PCI remain unclear.

Recently, several risk factors for CIN have been identified. Among them, contrast volume (CV) is a major factor for CIN.[6–8] Therefore, several studies have investigated renal function–based safe limits of CV for preventing CIN. Previous studies have reported that the CV/creatinine clearance ratio independently predicts CIN in patients undergoing PCI with preexisting RD.[9,10] Moreover, the CV/estimated glomerular filtration rate (eGFR) ratio is associated with CIN in patients

Clinical Perspective

What Is New?

- We found that the optimal cutoff value of the contrast volume/baseline estimated glomerular filtration rate ratio for persistent renal dysfunction after contrast-induced nephropathy was 3.45.

What Are the Clinical Implications?

- Persistent renal dysfunction after contrast-induced nephropathy, but not transient renal dysfunction, was independently associated with long-term mortality.
- In managing patients who develop persistent renal dysfunction after contrast-induced nephropathy, intensive renal function monitoring after the procedure and careful outpatient management may improve long-term clinical outcomes.

with ST-segment–elevated myocardial infarction after primary PCI.[11,12] However, the safe volume of contrast media for preventing persistent RD after CIN has not been investigated. Furthermore, whether the CV/eGFR ratio is independently associated with persistent RD is unclear in patients who undergo primary PCI for AMI.

This study aimed to identify predictors of persistent RD after CIN and the association of persistent RD on the long-term prognosis in patients who undergo primary PCI for AMI.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

This study was a single-center, retrospective, observational study. In the present study, patients with AMI who underwent primary PCI were enrolled at Miyazaki Prefectural Nobeoka Hospital from April 2008 to May 2016. Figure 1 shows the enrollment and exclusion criteria and patient flow through the study. Patients with end-stage renal failure with hemodialysis were excluded from this study. Patients who presented with cardiogenic shock before the procedure (Killip class IV), cardiopulmonary arrest (contains ventricular fibrillation), and in-hospital death were excluded. Patients' characteristics and procedural data were recorded retrospectively for all patients. Patients' characteristics included age, sex, body mass index, diabetes mellitus, hypertension, dyslipidemia, hyperuricemia, anemia, smoking, history of stroke, use of statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium blockers, β blockers, and diuretics. AMI was defined as chest pain, any change in an ECG, and an abnormal increase in serum levels of creatinine kinase or troponin T.

Coronary disease characteristics included ST-segment–elevated myocardial infarction or non–ST-segment–elevated myocardial infarction, a history of PCI, a history of myocardial infarction, a history of congestive heart failure, and the left ventricular ejection fraction. Procedural characteristics included the culprit vessel (left anterior descending artery, left circumflex artery, right coronary artery, or left main trunk), number of diseased vessels (single-vessel or multivessel disease), Killip class >I, CV, CV/baseline eGFR ratio, intravascular ultrasound use, procedural success, slow flow (thrombolysis in myocardial infarction flow grade <3), and use of intra-aortic balloon pumping. Laboratory measures included serum creatinine levels (baseline, within 48 hours, up to 2 weeks after the procedure, and 9–12 months after the procedure), baseline eGFR, and levels of hemoglobin, uric acid, blood urea nitrogen, and peak creatine phosphokinase after the procedure. The eGFR was calculated using the Japanese Modification of Diet in Renal Disease study equation, released by the Japanese Society of Nephrology[13]: eGFR (men)=$194\times$serum creatinine levels$^{1.094}\times$age$^{0.287}$ and eGFR (women)=eGFR (men)$\times$0.739. The maximum acceptable contrast dose was calculated as follows: [5$\times$body weight (kg)]/baseline creatinine level.[14] We calculated the Mehran risk score,[15] which is widely used for predicting CIN, evaluating the following clinical and procedural variables: hypotension (5 points), intra-aortic balloon pumping (5 points), congestive heart failure (5 points), diabetes mellitus (3 points), age >75 years (4 points), anemia (3 points), eGFR (6 points for an eGFR <20 mL/min per 1.73 m^2, 4 points for an eGFR from 20–40 mL/min per 1.73 m^2, and 2 points for an eGFR from 40 to 60 mL/min per 1.73 m^2), and volume of contrast (1 point for each 100 mL).

Definition of Persistent and Transient RD

Renal function was assessed on admission (before PCI) as baseline, within 48 hours after PCI, and up to 2 weeks and at 9 to 12 months after PCI. Persistent RD was defined as residual impairment of creatinine levels ≥0.5 mg/dL or ≥25% over 2 weeks compared with baseline.[16–18] Transient RD was defined as an absolute increase in creatinine levels from baseline of ≥0.5 mg/dL or ≥25% within 48 hours after the procedure and returned to serum creatinine levels <0.5 mg/dL or <25% above the baseline within 2 weeks. No CIN was defined as no significant increase in creatinine levels (<0.5 mg/dL or <25%) within 48 hours after the procedure. Patients with preexisting chronic renal failure (eGFR <60 mL/min) were applied postprocedural hydration therapy until 12 hours after PCI at the discretion of each physician.

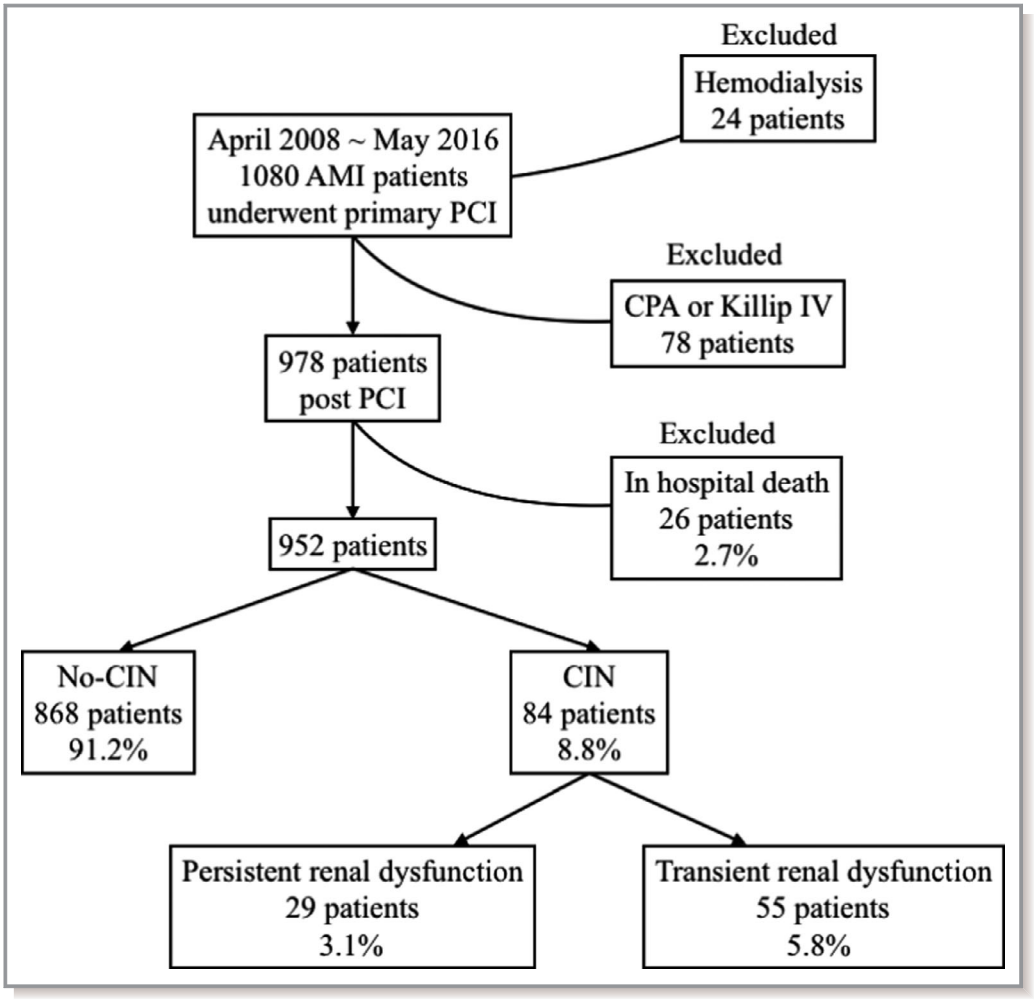


Figure 1. Patient flow in the study. Contrast-induced nephropathy (CIN) was defined as an increase in serum creatinine levels ≥0.5 mg/dL or ≥25% from baseline within 48 hours after percutaneous coronary intervention (PCI). Persistent renal dysfunction was defined as residual impairment of renal function for >2 weeks after the procedure. In transient renal dysfunction, serum creatinine levels returned to baseline within 2 weeks. AMI indicates acute myocardial infarction; CPA, cardiopulmonary arrest.

End Points

The primary end point of this study was mortality up to 3 years of follow-up. The secondary end point was a composite of death, new onset of hemodialysis-dependent renal failure, stroke, and myocardial infarction. Clinical follow-up was performed with outpatient visit or telephone interview.

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the distribution of continuous data. Normally distributed data are expressed as mean±SD, whereas those with skewed distribution are expressed as the median value with interquartile range. Categorical data are shown by frequencies and percentages. Differences between 2 groups were tested with the χ^2 test or Fisher exact test for categorical variables. Differences in continuous variables were analyzed by the unpaired *t* test or Mann-Whitney *U* test, as appropriate. For multiple groups' comparisons, 1-way ANOVA or Kruskal-Wallis test was used for continuous variables, followed by multiple comparisons with the Bonferroni method, as appropriate. Multiplicity issues resulting from pairwise comparisons were approached with the Bonferroni adjustment (yielding a significance threshold of 0.017). Receiver-operator characteristic analysis was performed to determine the optimal cutoff point for the CV/eGFR ratio and Mehran risk score for predicting persistent RD after CIN. We determined the optimal cutoff value of CV/eGFR by identifying the point on the curve closest to the upper left-hand corner (0, 1) point. An improvement in risk scores on the prediction of persistent RD was evaluated using the net reclassification index and integrated discrimination index.

Univariable logistic regression analysis was performed for significant clinical factors for screening. Multivariable logistic regression analysis was used to identify correlates of persistent

Table 1. Baseline Patients' and Disease Characteristics

Characteristics	No CIN (n=868)	Transient RD (n=55)	Persistent RD (n=29)	*P* Value
Age, y	69.7±12.2	72±12.5	73.2±11.4	0.14
Age >75 y, n (%)	343 (39.5)	24 (43.6)	14 (48.3)	0.55
Men, n (%)	632 (72.8)*	36 (65.5)	14 (48.3)*	0.009
Body mass index, kg/m^2	23.6±3.76	23.6±3.7	23.1±4.8	0.81
ST-segment–elevated myocardial infarction, n (%)	584 (62.3)	44 (80)	17 (58.6)	0.085
Hypertension, n (%)	626 (72.1)	42 (76.4)	21 (72.4)	0.81
Diabetes mellitus, n (%)	274 (31.6)*	22 (40)	16 (55.2)*	0.015
Dyslipidemia, n (%)	545 (62.8)	36 (65.5)	19 (65.5)	0.91
Smoke, n (%)	470 (54.1)	30 (54.5)	16 (55.2)	0.99
Hyperuricemia, n (%)	62 (7.1)	4 (7.3)	2 (6.9)	0.99
History of stroke, n (%)	76 (8.6)	4 (7.3)	4 (13.8)	0.32
History of PCI, n (%)	109 (12.6)*†	1 (1.8)†‡	10 (34.5)*‡	<0.001
OMI, n (%)	81 (9.3)	1 (1.8)‡	5 (17.2)‡	0.048
Congestive heart failure, n (%)	21 (4)*†	8 (15.1)†	5 (17.9)*	<0.001
Contrast volume, mL	143.2±50.5	153.0±45.9	148.6±52.2	0.33
MACD, mL	351±112.8*	349.1±142.1‡	258.8±155.6*‡	<0.001
Exceed MACD, n (%)	32 (3.7)*	2 (3.8)	5 (17.2)*	0.008
eGFR, mL/min per 1.73 m^2	64.2±19.6*	61.7±23.3‡	45.4±22.9*‡	<0.001
CV/eGFR ratio	2.49±1.49*	2.98±1.99	4.10±2.51*	<0.001
CV/eGFR ratio >3.45, n (%)	198 (22.8)*	15 (27.3)‡	19 (65.5)*‡	<0.001
Mehran score	6.6±4.2*†	8.7±5.2†	11.2±5.5*	<0.001
eGFR <30 mL/min per 1.73 m^2, n (%)	40 (4.6)*	6 (10.9)	9 (31)*	<0.001
Hemoglobin, g/dL	13.9±2.1*	13.6±2.5	12.4±2.4*	0.001
BUN, mg/dL	17.3±6.82*	21.7±15.2	25.3±13.2*	<0.001
UA, mg/dL	5.8±1.59	5.93±1.64	5.86±1.51	0.75
Potassium, mEq/L	4.07±0.51	4.13±0.58	4.13±0.59	0.68
Peak CPK, IU/L	1050 (270–5220)	1652 (752–4032)	1239 (452–2731)	0.16
EF, %	57.3±10.1†	53.8±10.9†	51.1±13.6	<0.001
Anemia, n (%)	212 (24.5)	18 (32.7)	12 (41.4)	0.05
Slow flow, n (%)	139 (16)	14 (25.5)	6 (20.7)	0.16
Killip >1, n (%)	46 (5.3)*†	17 (30.9)†	9 (31)*	<0.001
LAD, n (%)	398 (45.6)	33 (60)	18 (62.1)	0.033
RCA, n (%)	261 (30)	14 (25.5)	6 (20.7)	0.44
LCX, n (%)	239 (27.6)	8 (14.5)	8 (27.6)	0.11
LMT, n (%)	23 (2.6)	4 (7.3)	0 (0)	0.4
Multivessel disease, n (%)	357 (41.1)	25 (45.5)	14 (48.3)	0.62
IVUS use, n (%)	856 (98.6)	55 (100)	28 (96.6)	0.45
Intra-aortic balloon pumping, n (%)	31 (3.6)	4 (7.3)	4 (13.8)	0.008
EF <40%, n (%)	43 (5)	5 (9.1)	4 (13.8)	0.024
Procedural success, n (%)	849 (97.8)	52 (94.5)	28 (96.6)	0.17
Statin, n (%)	685 (79.6)	39 (71)	21 (77.8)	0.31

Continued

Table 1. Continued

Characteristics	No CIN (n=868)	Transient RD (n=55)	Persistent RD (n=29)	*P* Value
ACEI/ARB, n (%)	689 (79.5)	49 (89.1)	23 (79.3)	0.22
Calcium channel blocker, n (%)	199 (23)	11 (20)	10 (34.5)	0.3
β Blocker, n (%)	272 (31.4)†	26 (47.3)†	15 (51.7)	0.005
Diuretics, n (%)	76 (8.8)*†	19 (34.5)†	11 (37.9)*	<0.001

Data are mean±SD, unless otherwise indicated. Peak CPK is expressed as the median (interquartile range). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BUN, blood urea nitrogen; CIN, contrast-induced nephropathy; CPK, creatine phosphokinase; CV, contrast volume; EF, ejection fraction; eGFR, estimated glomerular filtration rate; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main trunk; MACD, maximum acceptable contrast dose; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; RD, renal dysfunction, UA, uric acid.
*No CIN vs persistent CIN, *P*<0.017 (Bonferroni correction).
†No CIN vs transient CIN, *P*<0.017 (Bonferroni correction).
‡Transient CIN vs persistent CIN, *P*<0.017 (Bonferroni correction).

RD after primary PCI. Results are presented as odds ratios with 95% CIs. Multivariable logistic regression analyses were conducted with 3 forced inclusion models, including important well-known risk factors such as age >75 years, female sex, anemia, diabetes mellitus, or Killip >1. In addition, to confirm the robustness of the result, other forced inclusion models were

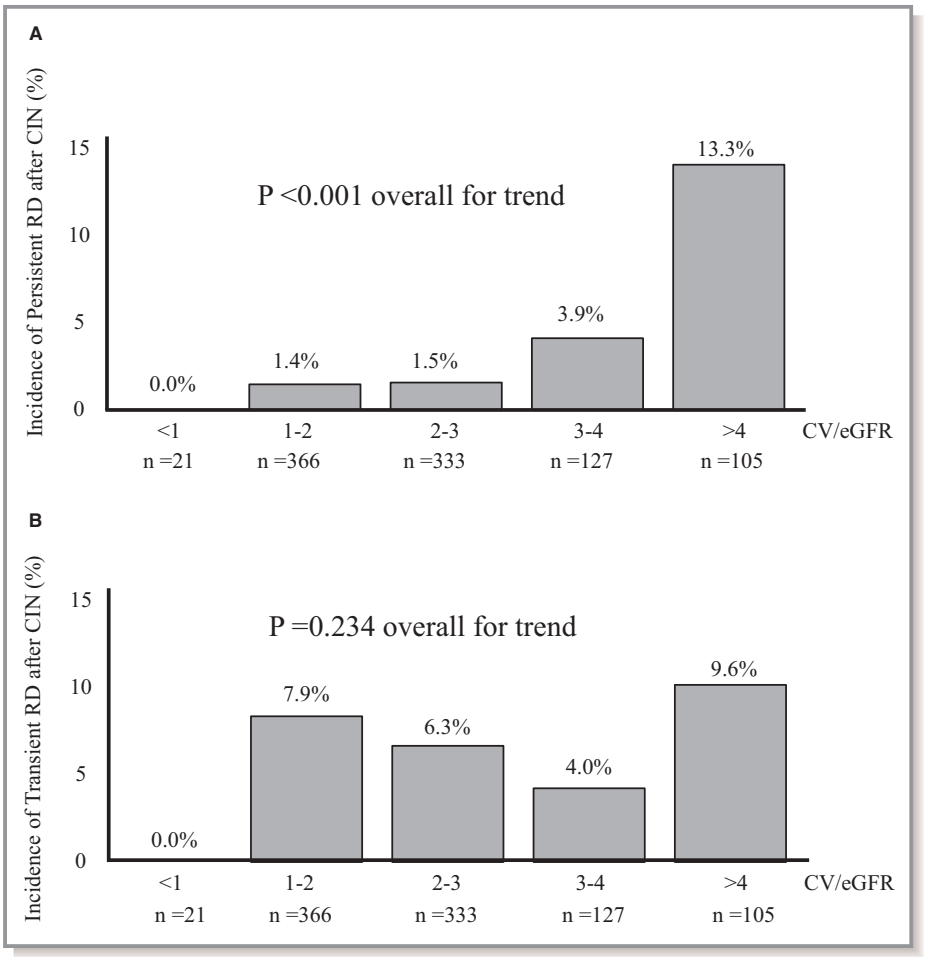
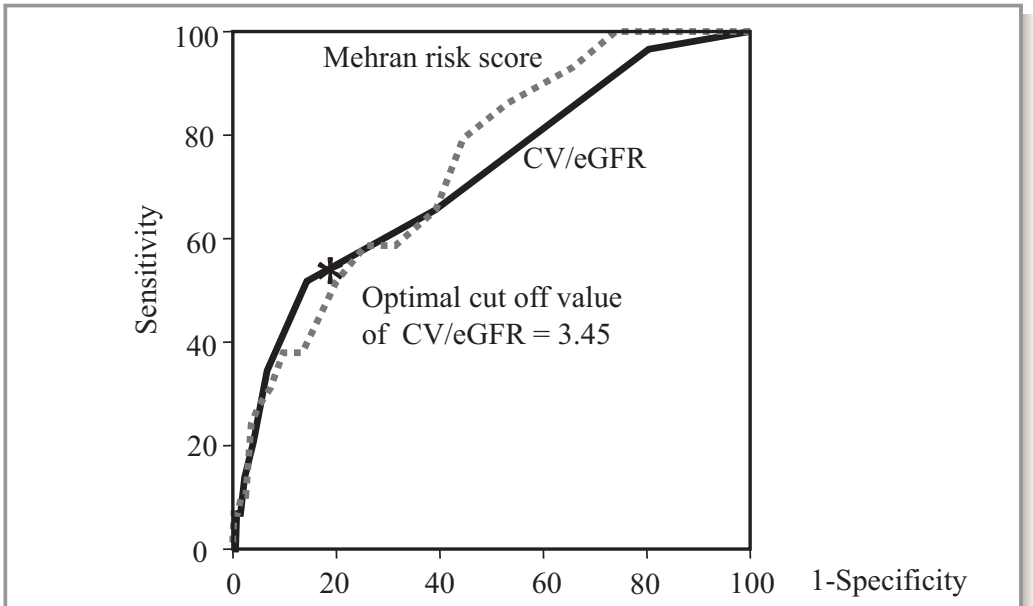


Figure 2. **A**, Relationship between the contrast volume/baseline estimated glomerular filtration rate (CV/eGFR) ratio and persistent renal dysfunction. The association between the CV/eGFR ratio and the percentage of patients with persistent renal dysfunction after primary percutaneous coronary intervention was highly significant (*P*<0.001). **B**, Relationship between the CV/eGFR ratio and transient renal dysfunction. The association between the CV/eGFR ratio and the percentage of patients with transient renal dysfunction after primary percutaneous coronary intervention was not significant (*P*=0.234). CIN indicates contrast-induced nephropathy; RD, renal dysfunction.



	CV/eGFR	Mehran risk score	P value
AUC (95% CI)	0.74 (0.64, 0.84)	0.74 (0.66, 0.82)	0.945
NRI (95% CI)	Ref	0.2851 (-0.0837, 0.654)	0.130
IDI (95% CI)	Ref	0.0199 (-0.0073, 0.0471)	0.151

Figure 3. Receiver-operator characteristic curve for predicting persistent contrast-induced nephropathy (CIN) using the contrast volume/baseline estimated glomerular filtration rate (CV/eGFR) ratio and Mehran risk score. Receiver-operator characteristic analysis showed that the optimal cutoff value for the CV/eGFR ratio was 3.45 for predicting persistent renal dysfunction after CIN. AUC indicates area under the curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

performed using variables with $P<0.05$ on the univariable analysis (Data S1, Table S1). Survival curves were generated with the Kaplan-Meier method, and statistical assessments among the 3 groups were performed using the log-rank test. The Bonferroni correction was used to analyze differences among 3 groups and yielded a significance threshold of 0.017. Cox regression proportional hazard analysis was used to assess hazard ratios (HRs) with 95% CIs for comparing patients with persistent RD with those with transient RD, and without CIN. Multivariate Cox proportional hazard regression models were used to assess HRs with 95% CIs for comparing patients with persistent RD and those without persistent RD (transient RD and no CIN groups). All statistical analyses were conducted using the Statistical Package for Social Sciences software, version 20 (IBM Corp, Armonk, NY).

Table 2. Univariable Logistic Regression Analyses for Persistent RD

	Univariable Analysis		
Variable	OR	95% CI	*P* Value
Female sex	2.80	1.34–6.00	0.006
Age >75 y	1.41	0.68–2.96	0.36
CV/eGFR ratio >3.45	6.88	3.24–14.6	<0.001
Diabetes mellitus	2.61	1.24–5.49	0.012
Killip >1	6.14	2.69–14.1	<0.001
Anemia	2.14	1.01–4.54	0.048
eGFR <60 mL/min per 1.73 m^2	5.48	2.21–13.6	<0.001
History of PCI	3.89	1.76–8.58	0.01
Use of diuretics	5.31	2.44–11.6	<0.001

CV indicates contrast volume; eGFR, estimated glomerular filtration rate; OR, odds ratio; PCI, percutaneous coronary intervention; RD, renal dysfunction.

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki, established by the World Medical Association, and *Ethical Principles in Clinical Studies*, published by the Ministry of Health, Labour and Welfare of Japan. This study was approved by the institutional review board of Miyazaki Prefectural Nobeoka Hospital. Written informed consent was obtained from each patient or family of the subject.

Table 3. Multivariable Logistic Regression Analyses for Persistent RD

Variable	Multivariable Analysis		
	OR	95% CI	*P* Value
Model 1			
CV/eGFR ratio >3.45	5.97	2.78–12.8	<0.001
Female sex	2.66	1.24–5.72	0.012
Diabetes mellitus	2.37	1.10–5.11	0.028
Model 2			
CV/eGFR ratio >3.45	6.47	2.93–14.3	<0.001
Anemia	1.42	0.62–3.23	0.41
Age >75 y	0.88	0.40–1.97	0.76
Model 3			
CV/eGFR ratio >3.45	5.41	2.49–11.8	<0.001
Killip >1	4.25	1.78–10.2	0.001
Diabetes mellitus	2.16	1.00–4.67	0.05

CV indicates contrast volume; eGFR, estimated glomerular filtration rate; OR, odds ratio; RD, renal dysfunction.

Results

Patients' Characteristics

Among 1080 consecutive patients, 128 were excluded (24 because of hemodialysis, 78 because of cardiogenic shock or cardiopulmonary arrest on arrival, and 26 because of in-hospital death). Ultimately, a total of 952 consecutive patients were included in the present study, of whom 682 (71.6%) were men and 645 (67.8%) had ST-segment–elevated myocardial infarction. CIN was observed in 84 patients (8.8%). In all patients who developed CIN, serum creatinine was measured within 2 weeks after primary PCI. Persistent RD (defined as residual impairment of renal function over 2 weeks) was observed in 29 patients (3.1%), and baseline eGFR levels had returned to baseline in 55 patients (5.8%); this was categorized as transient RD (Figure 1). Number of days after the primary PCI that the final creatinine was measured in 2 weeks was 8.3±2.9 for persistent RD and 8.7±3.0 for transient RD. Baseline clinical, biochemical, and procedural characteristics of the enrolled patients are shown in Table 1. Patients who developed persistent RD were more likely to be women, more frequently had diabetes mellitus, a history of PCI, and lower baseline eGFR levels, and had a higher CV/eGFR ratio and a higher rate of exceeding maximum acceptable contrast dose compared with those who did not develop CIN after PCI. In addition, patients who developed persistent RD had a higher Killip class and more frequently had congestive heart failure and use of a diuretic agent compared with those who did not develop CIN after PCI. Moreover, patients with persistent RD showed significantly lower baseline eGFR levels and had a higher rate of a history of PCI compared with those with transient RD. There were no significant differences in CV among the 3 groups (no CIN: 143.3±50.5 mL; transient RD: 153±45.9 mL; persistent RD: 148.6±52.2 mL). Other clinical characteristics, such as the culprit vessel and number of diseased vessels, procedural success rate, intravascular ultrasound use, and statin and angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker administration rates, were similar among the 3 groups.

CV/eGFR Ratio and Persistent CIN

The mean CV/eGFR ratio was 2.49±1.49 in patients without CIN, 2.98±1.99 in those with transient RD, and 4.10±2.51 in those with persistent RD. There was a significant association between higher CV/eGFR ratio values and occurrence of persistent RD after CIN (*P*<0.001 overall for trend) (Figure 2A). However, there

Table 4. Long-Term Clinical Outcomes of the 3 Groups

End Point	No CIN (n=868)		Transient RD (n=55)		Persistent RD (n=29)		*P* Value
	No. (%)	Incidence (1000 Person-Years)	No. (%)	Incidence (1000 Person-Years)	No. (%)	Incidence (1000 Person-Years)	
Death	35 (4.0)	24.7	1 (1.8)	10.1	8 (27.6)	147.1	<0.001
Dialysis	3 (0.3)	2.1	1 (1.8)	10.1	3 (10.3)	55.2	<0.001
MI	1 (0.1)	0.7	0 (0)	0.0	0 (0)	0.0	0.95
Stroke	4 (0.5)	2.8	2 (3.6)	20.3	1 (3.4)	18.4	0.006
Combined end point of mortality, dialysis, stroke, and MI	42 (4.8)	29.6	4 (7.3)	40.6	11 (37.9)	202.3	<0.001

CIN indicates contrast-induced nephropathy; MI, myocardial infarction; RD, renal dysfunction.

was no significant association between the CV/eGFR ratio and occurrence of transient RD after CIN (P=0.234 overall for trend) (Figure 2B).

Predictors of Persistent CIN

Receiver-operator characteristic curve analysis showed that the area under the curve for the Mehran risk score was 0.74 (95% CI, 0.66–0.82) for persistent RD after CIN. For the CV/eGFR ratio, the area under the curve was similar to the Mehran risk score for persistent RD after CIN (0.74; 95% CI, 0.64–0.84; P=0.95). The CV/eGFR had a similar predictive value to the Mehran risk score (net reclassification improvement: 0.29 [P=0.13]; integrated discrimination improvement: 0.02 [P=0.15]) (Figure 3).

Receiver-operator curve analysis also showed fair discrimination between patients with and those without persistent RD at a CV/eGFR ratio of 3.45 (Figure 3). At this value, the sensitivity and specificity of persistent RD were 56.7% and 76.7%, respectively. Univariable logistic regression indicated that a CV/eGFR ratio >3.45 was a highly significant predictor of persistent RD (odds ratio, 6.88; 95% CI, 3.24–14.63) (Table 2). Multivariable analysis showed that a CV/eGFR ratio >3.45 was significantly and independently associated with persistent RD after adjusting for other potential risk factors (Table 3).

Long-Term Prognosis

The median follow-up period was 1.37 years (interquartile range, 0.81–3.0 years), and the mean follow-up period was 1.66±1.1 years. The incidence rates of death and de novo introduction of hemodialysis or stroke in each group during the follow-up period are shown in Table 4. Serum creatinine was measured at 9 to 12 months after PCI in 801 patients (84.1%) (26 patients [89.7%] with persistent RD, 44 patients [80.0%] with transient RD, and 731 patients [84.2%] with no CIN). Serum creatinine at 9 to 12 months after PCI was significantly higher in patients with persistent RD and transient RD than those with no CIN (persistent RD: 2.51±2.05; transient RD: 1.29±1.18; no CIN: 1.01±0.63 mg/dL [P<0.001]).

Table 5. Characteristics and Long-Term Clinical Outcomes of Patients With or Without Periprocedural Complications

Variables	Patients With Periprocedural Complications (n=13)	Patients Without Periprocedural Complications (n=939)	P Value
Age, y	79.3±8.7	69.8±12.2	0.005
Men, n (%)	7 (63.6)	675 (71.8)	0.15
ST-segment–elevated myocardial infarction, n (%)	9 (69.2)	636 (67.7)	0.91
Diabetes mellitus, n (%)	6 (46.2)	306 (32.6)	0.30
OMI, n (%)	1 (7.7)	86 (9.2)	0.86
Congestive heart failure, n (%)	0 (0)	34 (3.6)	0.44
Contrast volume, mL	165.7±75.3	143.6±49.9	0.31
eGFR, mL/min per 1.73 m^2	52.1±16.6	63.6±20.2	0.04
CV/eGFR ratio	3.46±2.03	2.55±1.58	0.04
Peak CPK, IU/L	979 (809–2871)	1276 (459–2806)	0.99
EF, %	52.1±16.6	57.0±10.3	0.08
Multivessel disease, n (%)	5 (38.5)	391 (41.6)	0.82
Intra-aortic balloon pumping, n (%)	1 (7.7)	38 (4.0)	0.51
Creatinine at baseline, mg/dL	1.15±0.38	1.07±0.45	0.49
Creatinine within 48 h after PCI, mg/dL	1.15±0.38	1.09±0.51	0.64
Creatinine at 9–12 mo after PCI, mg/dL	1.18±0.41	1.15±0.78	0.90
CIN, n (%)	1 (7.7)	83 (8.8)	0.89
Transient RD, n (%)	1 (7.7)	54 (5.8)	0.77
Persistent RD, n (%)	0 (0)	29 (3.1)	0.52

Data are mean±SD, unless otherwise indicated. Peak CPK is expressed as the median (interquartile range). CIN indicates contrast-induced nephropathy; CPK, creatine phosphokinase; CV, contrast volume; CV/eGFR, CV/baseline eGFR; EF, ejection fraction; eGFR, estimated glomerular filtration rate; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; RD, renal dysfunction.

We observed a total of 13 periprocedural complications, 2 cases of guidewire perforation, 3 cases of side branch occlusion, 3 cases of coronary dissection, 3 cases of hematoma at approach site, and 2 cases of iatrogenic stroke after PCI. There was no significant association between periprocedural complication and CIN (Table 5).

In Kaplan-Meier analysis at 3 years of follow-up, the incidence of death was significantly higher in patients with persistent RD after CIN than in those with transient RD after CIN (P=0.001) and in those without CIN (P<0.001). However, no significant difference was observed in the incidence of death between patients with transient RD and those with no CIN (P=0.36; Figure 4). Cox proportional hazard regression analysis showed that the risk of death was significantly higher in patients with persistent RD than in those with no CIN (HR, 5.78; 95% CI, 2.68–12.5; P<0.001). However, we observed no significant difference in the risk of death between patients with transient RD after CIN and those without CIN (P=0.37; Table 6). In Kaplan-Meier analysis, patients with persistent RD after CIN showed a significantly higher rate of the combined clinical end points of mortality, hemodialysis, and major cardiovascular events (stroke or myocardial infarction) at 3 years of follow-up than did patients with transient RD (P=0.005) and those with no CIN (P<0.001). However, we observed no significant difference in this rate between patients with transient RD after CIN and those without CIN (P=0.22; Figure 5). Cox proportional hazard regression analysis showed that the risk of the combined clinical end points was significantly higher in patients with persistent RD than in patients without CIN (HR, 6.69; 95% CI, 3.44–13.0; P<0.001) (Table 7).

Predictors of Long-Term Clinical Events

Among 952 patients with long-term follow-up, we investigated predictors of long-term clinical events using Cox regression analysis with 3 models. In model 1, persistent RD remained a significant risk factor for mortality after adjusting for baseline clinical variables (HR, 4.99; 95% CI, 2.30–10.8; P<0.001) (Table 6). Another independent predictor of mortality in multivariate analysis was age >75 years (HR, 2.59; 95% CI, 1.37–4.92; P=0.004) (Table 6). In model 3, age >75 years remained a significant risk factor for mortality after adjusting for baseline clinical variables (HR, 2.63; 95% CI, 1.37–5.02; P=0.004) (Table 6). Table 7 shows univariable and multivariable Cox proportional hazard regression models for combined end points. Persistent RD was an independent predictor for the combined clinical end points of mortality, hemodialysis, and major cardiovascular events (stroke or myocardial infarction) in model 1 (HR, 5.79; 95% CI, 2.96–11.3; P<0.001). Age >75 years remained a significant risk factor for mortality after adjusting for baseline clinical variables

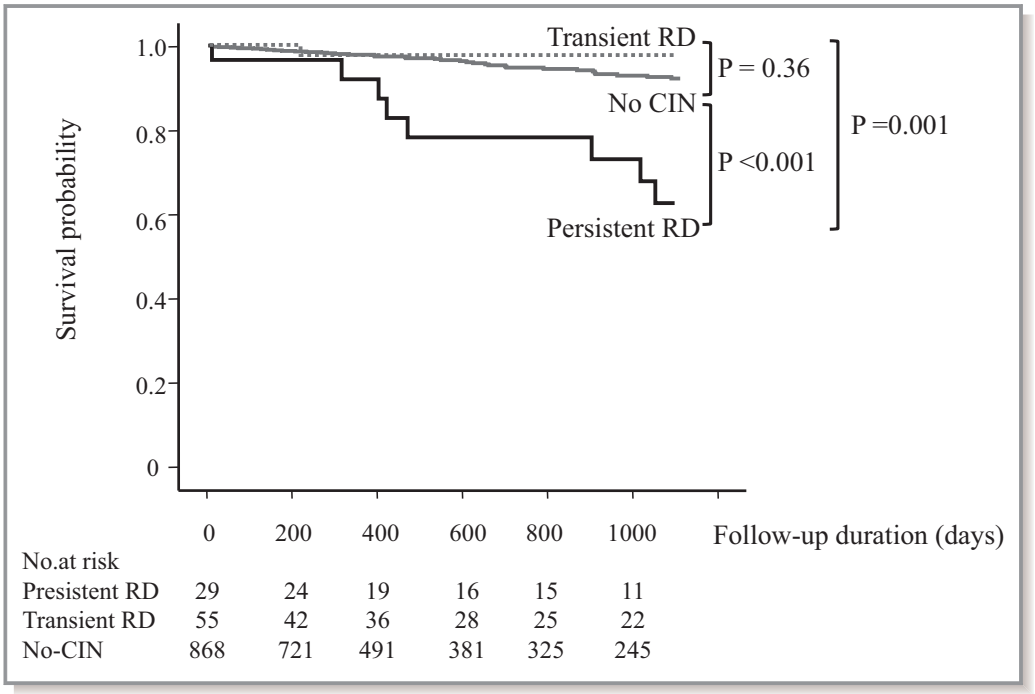


Figure 4. Survival curves (Kaplan-Meier analysis) for mortality. The incidence of death was significantly higher in patients with persistent renal dysfunction (RD) after contrast-induced nephropathy (CIN) than in patients with transient RD after CIN (P=0.001) and in those without CIN (P<0.001). However, this relationship between patients with transient RD and those with no CIN was not significant (P=0.36).

Table 6. Univariable and Multivariable Cox Proportional Hazard Regression Models for Mortality

	Univariable Analysis			Multivariable Analysis								
				Model 1			Model 2			Model 3		
Variables	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Renal category												
No CIN	Reference	Reference	Reference	Reference	Reference	Reference	. . .	. . .	. . .	. . .	. . .	. . .
Transient RD	0.40	0.06–2.93	0.37	0.41	0.06–2.98	0.38	. . .	. . .	. . .	. . .	. . .	. . .
Persistent RD	5.78	2.68–12.5	<0.001	4.99	2.30–10.8	<0.001	. . .	. . .	. . .	. . .	. . .	. . .
CV/eGFR ratio >3.45	1.67	0.86–3.25	0.13	. . .	. . .	. . .	. . .	. . .	. . .	1.26	0.63–2.49	0.52
Mehran risk score	1.12	1.06–1.20	<0.001	. . .	. . .	. . .	1.06	0.96–1.17	0.25	. . .	. . .	. . .
Age >75 y	3.02	1.86–4.91	<0.001	2.59	1.37–4.92	0.004	2.10	0.98–4.51	0.06	2.63	1.37–5.02	0.004
Hypertension	0.94	0.49–1.80	0.85	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Diabetes mellitus	1.54	0.85–2.79	0.15	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Congestive heart failure	1.82	0.43–7.72	0.41	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Anemia	2.99	1.87–4.81	<0.001	1.43	0.76–2.69	0.26	1.19	0.55–2.56	0.67	1.48	0.78–2.81	0.23
Killip >1	2.29	0.97–5.41	0.06	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
LAD	1.73	0.95–3.15	0.08	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Multivessel disease	1.19	0.66–2.15	0.56	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
EF <40%	1.29	0.52–3.22	0.59	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .

CIN indicates contrast-induced nephropathy; CV/eGFR, contrast volume/baseline estimated glomerular filtration rate; EF, ejection fraction; HR, hazard ratio; LAD, left anterior descending artery; RD, renal dysfunction.

(model 1: HR, 2.12; 95% CI, 1.24–3.74; *P*=0.007; model 3: HR, 2.07; 95% CI, 1.18–3.62; *P*=0.01). Another independent predictor of combined end points in multivariate analysis was Mehran risk score (HR, 1.15; 95% CI, 1.06–1.24; *P*=0.001) in model 2.

Discussion

In the present study, persistent RD after CIN was independently associated with long-term mortality. However, there was no significant difference in long-term clinical outcomes between patients with transient RD after CIN and those without CIN. We also found that a CV/eGFR ratio >3.45 was an independent predictor of persistent RD after CIN.

CIN and Long-Term Clinical Outcomes

CIN is associated with increased in-hospital and long-term morbidity and mortality.[1,2] The specific pathophysiological association between CIN and long-term adverse events remains unclear. Patients who develop CIN have a greater burden of comorbidities (eg, diabetes mellitus, heart failure, and chronic kidney disease), each of which increase the risk of adverse events.[19,20] Therefore, development of CIN might be a surrogate of the burden of such comorbidities, resulting in long-term morbidity and mortality. However, the cause-and-effect relationship between CIN and long-term adverse events has been reported.[21,22] Previous study has shown that the intravascular ultrasound–guided minimum CV PCI significantly reduced CIN and induction of renal replacement therapy at 1 year in patients with advanced chronic kidney disease compared with the angiography-guided PCI group.[8] Further study is needed to confirm the effect of reducing the CV on long-term clinical outcomes.

CIN in Patients With AMI

Various studies have reported that the risk of CIN is significantly higher in patients with AMI undergoing primary PCI than in those undergoing elective PCI.[6,23–25] Impairment of systemic perfusion or hemodynamic instability, administration of a large volume of contrast medium, and impossibility of prophylactic hydration for renal protection are

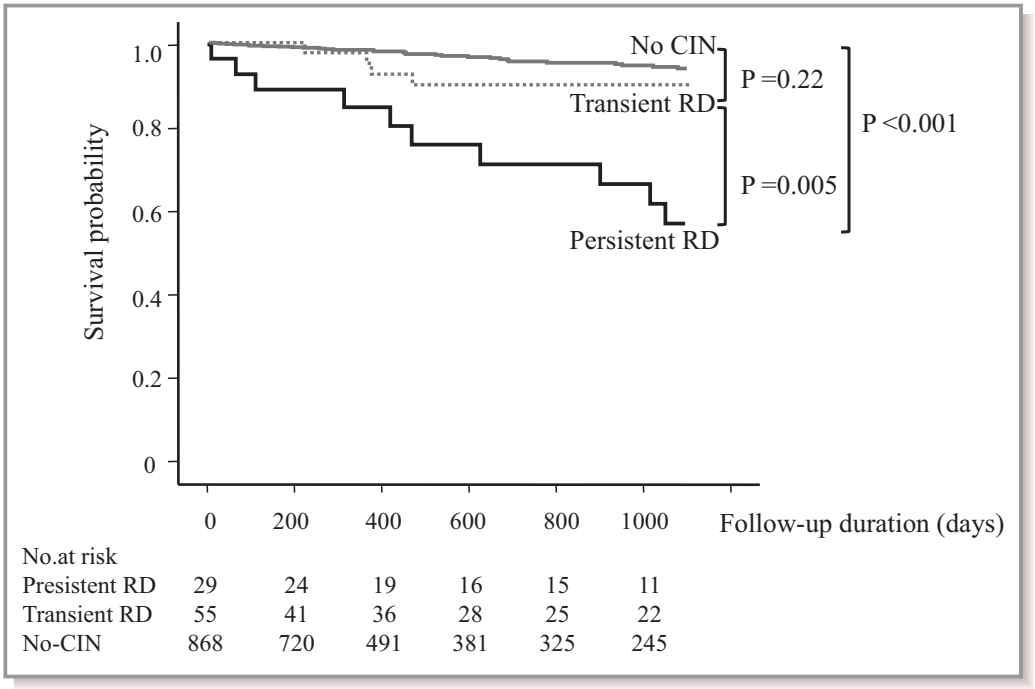


Figure 5. Survival curves (Kaplan-Meier analysis) for combined end points (mortality, hemodialysis, stroke, and myocardial infarction). The incidence of combined end points (mortality, hemodialysis, stroke, and myocardial infarction) was significantly higher in patients with persistent renal dysfunction (RD) after contrast-induced nephropathy (CIN) than in patients with transient RD (P=0.005) and those with no CIN (P<0.001). However, there was no significant difference between patients with transient RD after CIN and those with no CIN (P=0.22).

potential factors that contribute to a higher CIN risk in patients with AMI.[23]

Reversibility of Renal Function After CIN and Long-Term Clinical Outcomes

In the present study of 952 consecutive patients, the occurrence rate of CIN after primary PCI for AMI was up to 8.8%, and 34.5% of those patients did not shown a return to baseline renal function within 2 weeks. Persistent RD was associated with mortality and the combined clinical end points of mortality, hemodialysis, and major cardiovascular events (stroke or myocardial infarction). However, there was no significant difference in long-term clinical outcomes between patients with transient RD after CIN and those without CIN. CIN is generally considered transient, and creatinine levels peak several days after contrast medium administration and return to baseline within 2 weeks.[16–18] However, some patients with CIN experience persistent impairment of renal function; and this persistent RD correlates with a poor clinical prognosis.[4,5,26] Wi et al reported that patients with persistent RD after PCI for AMI experienced worse short- and long-term clinical outcomes than did those with transient RD.[26] Maioli et al reported that the incidence of death was significantly higher in patients with persistent RD than in patients with transient RD and those without CIN with preexistent moderate-to-severe RD.[5] However, Brown et al reported transient and persistent RD had a similar survival rate.[4] In these 3 studies of different cohorts, patients who developed transient RD had poorer clinical outcomes than did those without CIN. In contrast to these previous reports, we found no significant difference in long-term clinical outcomes between patients with transient RD after CIN and those without CIN. Although precise physiological differences between transient and persistent RD remain unclear, reversibility of renal function after development of CIN is thought to have significant implications for clinical outcomes; and our results support this hypothesis.

Predictors of Persistent CIN

In the present study, patients with persistent RD had a significantly higher rate of a history of PCI and lower baseline eGFR levels than did those with transient RD and those without CIN. These findings suggest that patients with persistent RD tend to have recurrent exposure to contrast media and have the possibility of previous CIN. The Mehran risk score is a classic model and is widely used for predicting CIN. This score includes 8 clinical and procedural variables, as follows: age >75 years, hypotension, congestive heart failure,

Table 7. Univariable and Multivariable Cox Proportional Hazard Regression Models for Combined End Points

	Univariable Analysis			Multivariable Analysis								
				Model 1			Model 2			Model 3		
Variables	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Renal category												
No CIN	Reference	Reference	Reference	Reference	Reference	Reference	. . .	. . .	. . .	. . .	. . .	. . .
Transient RD	1.34	0.48–3.74	0.58	1.33	0.48–3.73	0.58	. . .	. . .	. . .	. . .	. . .	. . .
Persistent RD	6.69	3.44–13.0	<0.001	5.79	2.96–11.3	<0.001	. . .	. . .	. . .	. . .	. . .	. . .
CV/eGFR ratio >3.45	2.24	1.29–3.88	0.004	. . .	. . .	. . .	. . .	. . .	. . .	1.73	0.98–3.06	0.06
Mehran risk score	1.16	1.10–1.22	<0.001	. . .	. . .	. . .	1.15	1.06–1.24	0.001	. . .	. . .	. . .
Age >75 y	2.47	1.64–3.73	<0.001	2.12	1.24–3.74	0.007	1.24	0.65–2.34	0.52	2.07	1.18–3.62	0.01
Hypertension	1.12	0.71–1.79	0.62	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Diabetes mellitus	1.37	0.91–2.07	0.13	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Congestive heart failure	3.18	1.25–8.11	0.015	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Anemia	2.78	1.85–4.18	<0.001	1.55	0.89–2.69	0.12	0.92	0.47–1.78	0.80	1.56	0.89–2.74	0.13
Killip >1	1.71	0.91–3.21	0.10	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
LAD	1.08	0.72–1.63	0.7	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Multivessel disease	1.02	0.67–1.53	0.94	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
EF <40%	1.57	0.76–3.26	0.22	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .

CIN indicates contrast-induced nephropathy; CV/eGFR, contrast volume/baseline estimated glomerular filtration rate; EF, ejection fraction; HR, hazard ratio; LAD, left anterior descending artery; RD, renal dysfunction.

intra-aortic balloon pumping, serum creatinine, diabetes mellitus, anemia, and CV.[15] However, the Mehran risk score is evaluated only after the procedure. In our study, the CV/eGFR ratio had a similar predictive value to the Mehran risk score for persistent RD after CIN. Because CV is a modifiable factor, evaluating a safe CV on the basis of renal function is important before the procedure for preventing CIN. We also found that there was a significant association between a high CV/eGFR ratio and occurrence of persistent RD after CIN, but not with transient RD. Several studies investigated the safe volume of contrast media for preventing CIN. Laskey et al reported that the CV/creatinine clearance ratio was associated with CIN in patients after elective PCI and a CV/creatinine clearance ratio >3.7 was an independent predictor of CIN.[9] Celik et al reported that a CV/eGFR ratio >2 was significantly associated with CIN after primary PCI.[27] Moreover, Mager et al reported that a CV/eGFR ratio >3.7 predicted CIN and 1-year mortality in patients undergoing primary PCI after AMI.[28] In the present study, receiver-operator characteristic curve analysis showed fair discrimination between patients with and those without persistent RD at a CV/eGFR ratio of 3.45. In addition, a CV/eGFR ratio >3.45 was an independent predictor for persistent RD after use of diuretics, Killip class >I, and female sex. To the best of our knowledge, this is the first study to identify an association between the CV/eGFR ratio and persistent RD after primary PCI for AMI. Our results showed that a CV/eGFR >3.45 was simple but had similar predictive value to the Mehran risk score for persistent RD after CIN. We also found that there was no significant difference in CV among the 3 groups, which resulted in a high CV/eGFR ratio in patients with preexisting RD. Because CV is a modifiable factor for persistent RD, even in primary PCI for AMI, minimizing the dose of CV based on the eGFR might be useful for preventing persistent RD.

Management of Patients With Persistent RD

In agreement with a previous study,[4,5,26] our study showed that patients with persistent RD after CIN had poorer clinical

outcomes than did those without CIN. In this present study, patients with persistent RD more frequently had diabetes mellitus, a history of PCI, lower baseline eGFR levels, and congestive heart failure. It could be said that persistent RD after PCI would be a surrogate marker of risk accumulation that predicts poorer clinical outcomes. Furthermore, patients with persistent RD would have a potential risk of receiving more conservative therapy for cardiovascular disease, resulting in poorer clinical outcomes.

Therefore, in managing patients who develop persistent RD after CIN, early clinical follow-up and careful management have the potential to improve long-term clinical outcomes. Further randomized, clinical trials are required to confirm the clinical implications of persistent RD and transient RD on long-term morbidity and mortality.

Limitations

Several limitations to this study need to be considered. First, this study was a single-center, retrospective, observational study with a relatively small number of patients. In this present study, we found no significant difference in long-term clinical outcomes between patients with transient RD after CIN and those without CIN. These results could be biased for small sample size. A larger multicenter trial is required to confirm our findings. Second, hemodynamic instability caused by AMI may have affected baseline renal function. Furthermore, we could not report on prophylactic treatment because the hydration therapy after primary PCI was left to the discretion of each interventional cardiologist.

Conclusions

In patients with AMI treated with primary PCI, persistent RD after CIN, but not transient RD, is independently associated with long-term mortality. Furthermore, a CV/eGFR ratio >3.45 is a significant independent predictor of persistent RD after CIN.

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Disclosures

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Supplemental Material

Data S1.

A CV/eGFR ratio >3.45 remained to be significantly and independently associated with persistent RD in multivariable logistic regression analysis after adjusting for each 2 of 4 clinical variables; female sex, a history of PCI, use of a diuretic agent, Killip class >1 (Table S1).

Table S1. Multivariable Logistic Regression Analyses for Persistent RD.

	Multivariable analysis		
Variable	OR	95%CI	P value
Model 1			
CV/eGFR >3.45	5.81	2.69-12.58	<0.001
Female sex	2.64	1.22-5.71	0.013
History of PCI	3.52	1.53-8.09	0.003
Model 2			
CV/eGFR >3.45	5.80	2.68-12.56	<0.001
Female sex	2.28	1.05-4.94	0.037
Use of diuretics	3.92	1.73-8.87	0.001
Model 3			
CV/eGFR >3.45	5.45	2.50-11.87	<0.001
Female sex	2.29	1.06-5.00	0.036
Killip >1	4.00	1.66-9.63	0.002
Model 4			
CV/eGFR >3.45	5.57	2.56-12.12	<0.001
History of PCI	3.57	1.54-8.27	0.003
Use of diuretics	4.58	2.01-10.42	<0.001
Model 5			
CV/eGFR >3.45	5.27	2.41-11.54	<0.001
History of PCI	3.27	1.42-7.55	0.006
Killip >1	4.31	1.78-10.44	0.001

CV, contrast volume; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention.