

# Poor Prognosis of Contrast-Induced Nephropathy during Long Term Follow Up

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Contrast-induced nephropathy (CIN) is known to associate with poor prognosis. However, there have been few studies for long-term follow up. The purpose of this study was to know the prognosis of CIN during a 10-year follow up. We retrospectively analyzed 528 patients who underwent coronary angiography in Jeonbuk National University Hospital (South Korea, Jeonju) between Jan 2005 to Dec 2006. We excluded the patients who required regular dialysis before study enrollment. We compared adverse events in the no CIN (group I, n=485, 61.9±11.4 years, male 64.1%) and CIN (group II, n=43, 65.7±11.1 years, male 62.8%). Baseline clinical characteristics and cardiovascular risk factors were not different between the two groups except the post-procedure creatinine level (1.04 mg/dL vs 1.84 mg/dL, p=0.0001). The higher rates of all-cause death were observed in group II at 1-year (3.7% vs 13.9%, log-rank, p=0.001), 5-years (17.9% vs 34.9%, log-rank, p=0.003), and 10-years (25.3% vs 48.8%, log-rank, p=0.000). MACE was higher in group II at 1-year (3.9% vs 11.6%, log-rank, p=0.013), 5-years (6.8% vs 20.9%, log-rank, p=0.000) and 10-years (13.4% vs 27.9%, log-rank, p=0.000). In addition, CIN was an independent predictor for 10-year MACE (adjusted HR 3.432, 95% CI 1.314-8.965, p=0.012) after propensity score matching. The worse prognosis of CIN was continuously observed after the 10-year follow-up. Our data suggests that it is worthwhile to prevent the appearance of CIN in order to improve long-term results.

**Key Words:** Contrast Media; Acute Kidney Injury; Angiography; Heart

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## INTRODUCTION

Percutaneous coronary intervention (PCI) is an adequate treatment for coronary artery disease. However, one of the important complications of diagnostic coronary angiography or interventional procedures is the development of contrast-induced nephropathy (CIN).<sup>1-5</sup> CIN is a common reason of acute renal failure of in-hospitalization patients, responsible for 10% of in-hospitalization patients.<sup>6</sup>

In the general population, the incidence has been reported to be less than 2%.<sup>7</sup> In the high-risk populations, patients with chronic kidney disease (CKD), congestive heart failure, hypotension, diabetes mellitus, older age, anemia, the incidence has been reported as more than 20%.<sup>8-13</sup> CIN has been related to increased mortality and extended

length of hospital stay.<sup>14</sup>

However, the incidence of CIN reported after PCI varies widely, from 2% to 19%. This wide-ranging difference is considered to be the result of a single-center study or volume expansion protocols by hydration and less nephrotoxic iso-osmolar contrast agents. In addition, previous studies used different CIN definitions, making it difficult to compare the incidence of CIN.

Moreover, there have been few studies investigating long-term clinical follow-up for CIN patients up to 10-years. The aim of our study is to investigate the long-term outcome of CIN after more than 10-years.

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## MATERIALS AND METHODS

### 1. Study population

There were 956 patients who were treated with percutaneous coronary interventions at Jeonbuk National University Hospital from January 1<sup>st</sup>, 2005 to December 31<sup>th</sup>, 2006. This study was approved by the ethics committee and institutional review board of Chonbuk National University

**TABLE 1.** Baseline clinical characteristics

	Group I (n=485)	Group II (n=43)	p value
Age (years)	61.9±11.4	65.7±11.1	0.038
Male, n (%)	311 (64.1)	27 (62.8)	0.869
Risk factor (%)			
Hypertension, n (%)	247 (50.9)	23 (53.5)	0.754
Diabetes mellitus, n (%)	144 (29.7)	14 (32.6)	0.729
Hyperlipidemia, n (%)	95 (19.6)	7 (16.3)	0.691
Smoking, n (%)	239 (49.2)	19 (44.2)	0.187
Diagnosis (%)			
STEMI, n (%)	131 (27)	16 (37.2)	0.082
NSTEMI, n (%)	70 (14.4)	7 (16.3)	
UAP, n (%)	93 (19.1)	6 (14.0)	
SAP, n (%)	191 (39.4)	14 (32.6)	
Elective PCI, n (%)	346 (71.3)	33 (76.7)	0.027
Lab findings			
Pre-PCI Cr, mg/dL	1.20±1.44	1.28±1.24	0.337
Post-PCI Cr, mg/dL	1.04±0.94	1.84±1.54	0.000
Pre-eGFR	61.7±24.2	64.4±30.9	0.498
Total cholesterol, mg/dL	180.1±41.4	168.1±49.7	0.096
Triglyceride, mg/dL	137.3±96.1	114.8±65.6	0.076
HDL-C, mg/dL	41.1±11.8	35.2±9.3	0.005
LDL-C, mg/dL	111.9±37.9	108.4±37.2	0.599
LVEF, %	55.3±9.9	50.4±11.1	0.004
Medication			
Aspirin, n (%)	445 (91.8)	35 (81.4)	0.045
ACEI, n (%)	311 (64.1)	25 (58.1)	0.509
ARB, n (%)	57 (11.8)	3 (7.0)	0.457
CCB, n (%)	74 (15.3)	7 (16.3)	0.826

STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non-ST-segment elevation myocardial infarction, UAP: Unstable angina, SAP: Stable angina, PCI: percutaneous coronary intervention, Cr: Creatinine, eGFR: Estimated glomerular filtration rate, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, LVEF: left ventricular ejection fraction, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, CCB: calcium channel blocker.

**TABLE 2.** Long-term outcomes of Mortality

	Group I (n=485)			Group II (n=43)			p value
	All-cause death	Non-cardiac death	Cardiac death	All-cause death	Non-cardiac death	Cardiac death	
1-year, n (%)	18 (3.7)	13 (2.6)	5 (1)	6 (13.9)	4 (9.3)	2 (4.7)	0.001
5-year, n (%)	87 (17.9)	77 (15.5)	11 (2.2)	15 (34.9)	10 (23.3)	5 (11.6)	0.003
10-year, n (%)	123 (25.3)	98 (19.7)	27 (5.4)	21 (48.8)	14 (32.6)	7 (16.2)	0.000

Hospital (institutional review board file number: 2021-07-044). We excluded cardiogenic shock patients, patients without pre- and post-procedural serum creatinine levels, and end-stage renal disease patients who required regular dialysis before study enrollment. We retrospectively analyzed 528 patients who were treated with percutaneous coronary intervention and administered iodixanol (Visipaque®, GE Health Care, Cork, Ireland) as contrast agent. The study population was separated into two groups: group I (Non-CIN, 485 patients, mean age 61.9±11.4 years, male 64.1%) and group II (CIN, 43 patients, mean age 65.7±11.1 years, male 62.8%).

### 2. Definition and study endpoints

Contrast-induced nephropathy was defined as a rise in serum creatinine concentration of  $\geq 0.5$  mg/dL ( $>44$   $\mu$ mol/L) or a rise of 25% above baseline between 48 and 72 hours after contrast administration.<sup>15</sup> The glomerular filtration rate (eGFR) was calculated by the CKD-EPI creatinine equation.<sup>16</sup>

The primary endpoints were defined by a composite of death at the 1, 5, and 10-year marks. The secondary endpoints were defined by major adverse cardiac events (MACE) including cardiac death, non-fatal myocardial infarction (MI), and target vessel revascularization (TVR) at the 1, 5, and 10-year marks. Clinical events were investigated by medical record analysis. In order to verify the complete follow-up data, a unique personal identification code was used to obtain information about life status from the Korea National Health Insurance Corporation.

### 3. Coronary angiography and PCI

Coronary angiography was performed according to standard procedures. Primary PCI was performed by the on-call interventional team, based on the guidelines of the ACC/AHA/SCAI.<sup>17</sup> We enrolled patients who accepted pre-treatment with aspirin (at least 100 mg), clopidogrel (between 300 mg and 600 mg), and unfractionated or low molecular weight heparin before diagnostic coronary angiography and PCI. The hydration with physiologic (0.9%) saline was infused by 1 ml/kg/h for 12 hours before and after PCI to elective patients. However, several patients requiring emergent PCI could not accept enough hydration therapy (n=73, 14.7% in Group I vs n=10, 20.8% in Group II). According to standard clinical practice, coronary angiography was performed through the radial or femoral artery approach and used 5-7 French catheters. After the guidewire pass

**TABLE 3.** Long-term outcomes of MACE

	Group I (n=485)				Group II (n=43)				p value
	MACE	Non-fatal MI	TVR	Cardiac Death	MACE	Non-fatal MI	TVR	Cardiac Death	
1-year, n (%)	19 (3.9)	16 (3.2)	5 (1)	5 (1)	5 (11.6)	3 (6.9)	2 (4.7)	2 (4.7)	0.013
5-year, n (%)	33 (6.8)	24 (4.8)	8 (1.6)	11 (2.2)	9 (20.9)	4 (9.3)	3 (6.9)	5 (11.6)	0.000
10-year, n (%)	65 (13.4)	40 (8)	14 (2.8)	27 (5.4)	12 (27.9)	5 (11.6)	3 (6.9)	7 (16.2)	0.000

MACE: Major adverse cardiac events, MI: Myocardial infarction, TVR: Target vessel revascularization.

**TABLE 4.** Propensity score matching for baseline clinical characteristics

	Group I (n=86)	Group II (n=31)	p value
Age (years)	62.5±10.5	62.6±10.4	0.625
Male, n (%)	56 (65.1)	19 (61.3)	0.703
Risk factor (%)			
Hypertension, n (%)	46 (53.5)	14 (45.2)	0.426
Diabetes mellitus, n (%)	31 (36.0)	9 (29.0)	0.480
Hyperlipidemia, n (%)	12 (14.0)	6 (19.4)	0.671
Smoking, n (%)	43 (50)	14 (45.2)	0.611
Diagnosis (%)			
STEMI, n (%)	24 (27.9)	10 (32.3)	0.533
NSTEMI, n (%)	10 (11.6)	4 (12.9)	
UAP, n (%)	19 (22.0)	5 (16.1)	
SAP, n (%)	33 (38.4)	12 (38.7)	
Previous CVA, n (%)	3 (3.5)	2 (6.5)	0.607
Previous CKD, n (%)	1 (1.2)	1 (3.2)	0.461
Elective PCI, n (%)	62 (72.1)	21 (67.7)	0.149
Lab findings			
Pre-PCI Cr, mg/dL	1.01±0.71	1.29±1.40	0.279
Post-PCI Cr, mg/dL	0.98±0.67	1.89±1.93	0.009
Pre-eGFR	64.2±22.8	64.3±28.2	0.169
Total cholesterol, mg/dL	178.9±40.4	170.4±46.5	0.331
Triglyceride, mg/dL	131.9±113.6	125.8±69.6	0.780
HDL-C, mg/dL	42.2±10.5	35.3±8.3	0.001
LDL-C, mg/dL	109.5±33.7	109.1±37.7	0.958
LVEF, %	56.5±8.7	49.7±11.9	0.001
Medication			
Aspirin, n (%)	82 (95.3)	25 (80.6)	0.033
ACEI, n (%)	58 (67.4)	19 (61.3)	0.536
ARB, n (%)	13 (15.1)	2 (6.5)	0.356
CCB, n (%)	11 (12.8)	5 (16.1)	0.857

STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non-ST-segment elevation myocardial infarction, UAP: Unstable angina, SAP: Stable angina, CVA: cerebrovascular accident, CKD: chronic kidney disease, PCI: percutaneous coronary intervention, Cr: Creatinine, eGFR: Estimated glomerular filtration rate.

through the target lesion, stents were deployed after balloon dilatation. The appropriate diameter and length of the stents were carefully chosen to cover the target lesion. Each cardiologist carefully decided contrast media volume, interventional device and technique, supporting pharmacologic treatment, and post-dilatation therapy.

**TABLE 5.** Independent predictors of clinical events after Propensity score matching

	Hazard ratio (95% confidence interval)	p value
Predictors of MACE		
Age	0.969 (0.926-1.013)	0.162
Male	1.278 (0.402-4.064)	0.677
Diabetes mellitus	1.310 (0.503-3.416)	0.580
Contrast-Induced Nephropathy	3.432 (1.314-8.965)	0.012
Predictors of All-cause Death		
Age	1.039 (0.998-1.083)	0.065
Male	1.141 (0.480-2.712)	0.765
Hypertension	1.099 (0.461-2.625)	0.831
Diabetes mellitus	1.472 (0.658-3.291)	0.346
Contrast-Induced Nephropathy	3.624 (1.666-7.883)	0.001

Potential covariables included in the model: contrast-induced nephropathy, age, sex, diabetes mellitus, history of hypertension, previous myocardial infarction, Pre-estimated glomerular filtration rate, Previous congestive heart failure, Previous cerebrovascular accident, Previous chronic renal failure, Hyperlipidemia, smoking.

#### 4. Statistical analysis

All consecutive data are expressed by mean±standard deviation, and category data is expressed as percentages. For continuous variables, comparisons between the two groups were performed by means of a Student's t-test. Fischer's exact and chi-square tests were used for the evaluation of the categorical variables.

A multiple regression analysis was used to test whether primary differences between the two groups affected the different results after controlling for significantly different variables at the baseline. The Kaplan–Meier method and log-rank test were used for comparing all-cause death and MACE rates by the presence of CIN. We used propensity score matching to adjust for significant differences in patient baseline characteristics. A value of  $p < 0.05$  was considered statistically significant for all analyses. All statistical analyses were performed by SPSS-PC 19.0 (Statistical Package for the Social Sciences, SPSS-PC. Inc., Chicago, IL, USA) and the R programming language.

**RESULTS**

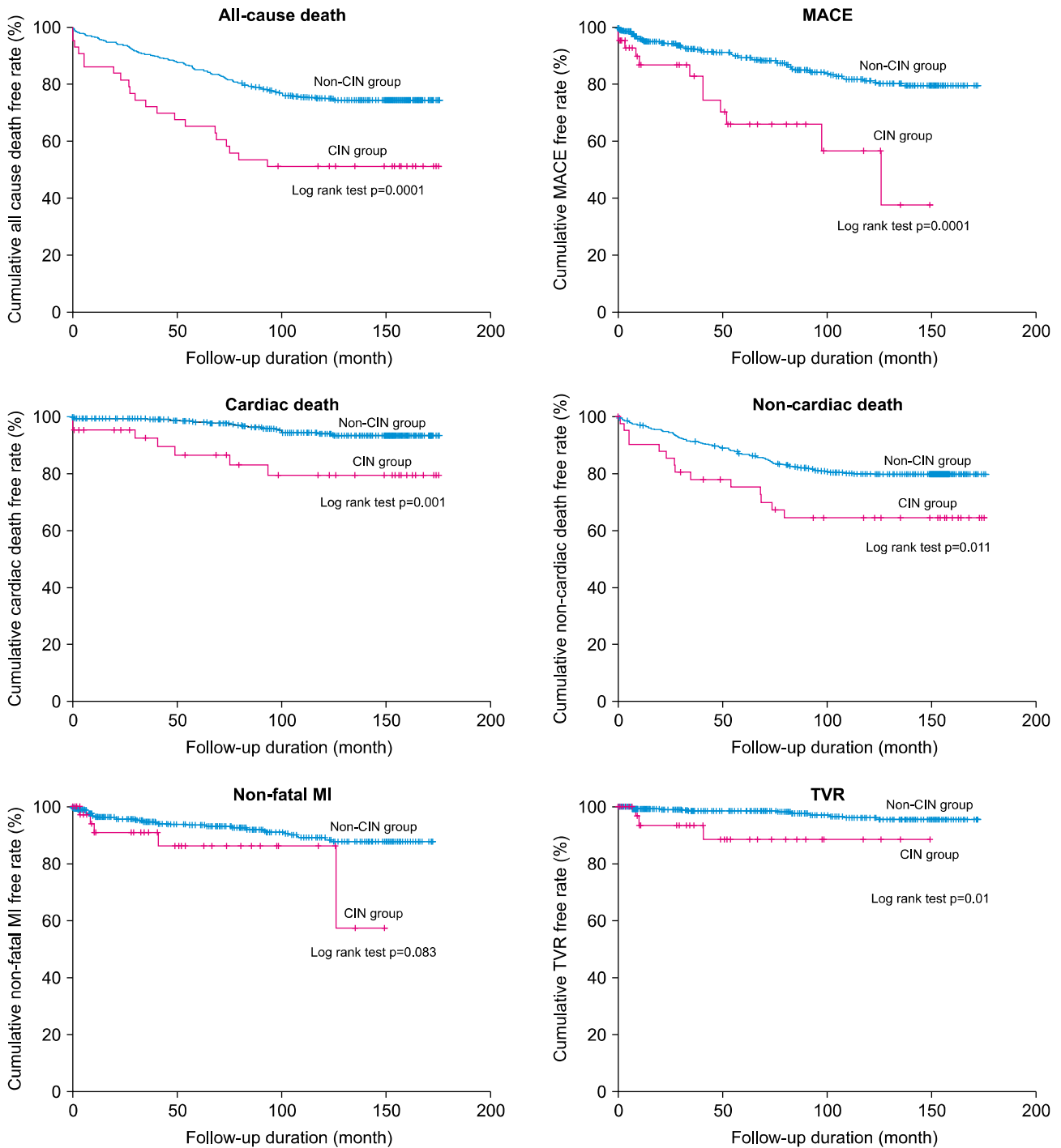
**1. Clinical and procedural characteristics**

Baseline clinical characteristics in this study are shown in Table 1. Patients in group II were more likely to have a lower left ventricular ejection fraction (group I vs group II, 55.3±9.9 vs 50.4±11.1) (p=0.004). The proportion of elective PCI in group II was significantly higher than in group I

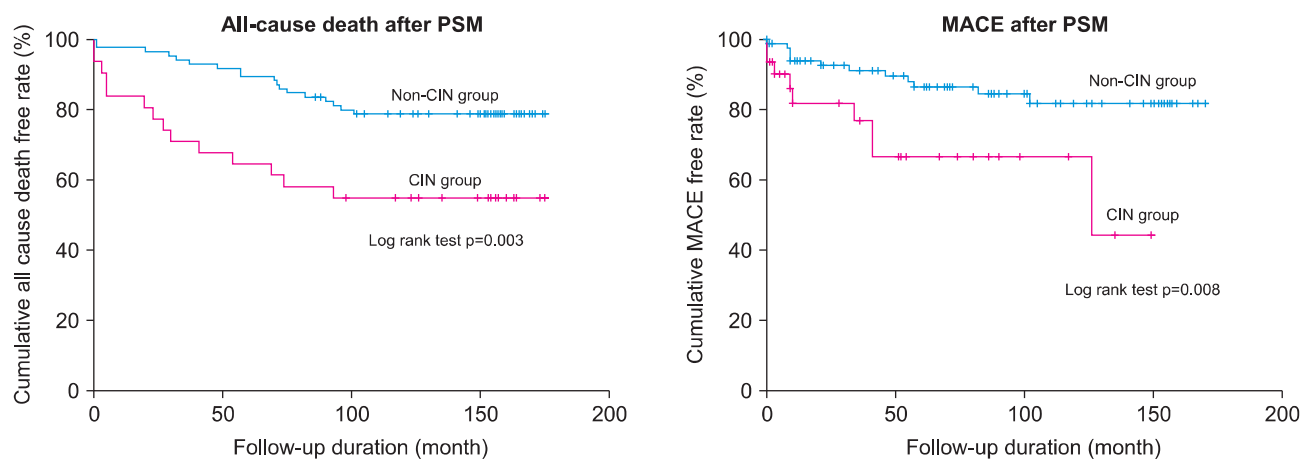
(71.3% vs 76.7%, p=0.027). Post-procedure creatinine levels in group II were higher than in group I (1.04 mg/dL vs 1.84 mg/dL, p=0.000).

**2. Long-term clinical follow-up**

There were significant differences in all-cause deaths and MACE between the two groups (Table 2, 3). Patients who suffered CIN had higher rates of all-cause death at



**FIG. 1.** Kaplan–Meier curves between contrast-induced nephropathy (CIN) and Non-CIN. MACE Major adverse cardiac events means the composite of myocardial infarction (MI), target vessel revascularization (TVR), and cardiac death.



**FIG. 2.** Kaplan-Meier curves after propensity score matching between contrast-induced nephropathy (CIN) and Non-CIN. PSM Propensity score matching, MACE Major adverse cardiac events means the composite of myocardial infarction (MI), target vessel revascularization (TVR), and cardiac death.

1-year (3.7% vs 13.9%, log-rank,  $p=0.001$ ), 5-years (17.9% vs 34.9%, log-rank,  $p=0.003$ ), and 10-years (25.3% vs 48.8%, log-rank,  $p=0.000$ ). MACE was lower in patients who did not develop CIN (Group I) compared to the patients who developed CIN (Group II) at 1-year (3.9% vs 11.6%, log-rank,  $p=0.013$ ), 5-years (6.8% vs 20.9%, log-rank,  $p=0.000$ ) and 10-years (13.4% vs 27.9%, log-rank,  $p=0.000$ ).

### 3. Propensity score matching

A total of 117 patients who were matched by propensity score matching (PSM) were analyzed (Table 4). Baseline clinical characteristics after PSM showed group II had a lower left ventricular ejection fraction (group I vs group II,  $56.5\pm 8.7$  vs  $49.7\pm 11.9$ ) ( $p=0.001$ ). Post-procedure creatinine levels in group II were higher than in group I (0.98 mg/dL vs 1.89 mg/dL,  $p=0.009$ ).

Moreover in multivariable analysis, CIN was an independent predictor of MACE (HR 3.432; 95%CI, 1.314-8.965;  $p=0.012$ ) and all-cause death (HR 3.624; 95%CI, 1.666-7.883;  $p=0.001$ ) (Table 5).

Kaplan-Meier analysis showed that CIN was associated with the risk of all-cause deaths, cardiac death, non-cardiac death, and MACE (Fig. 1). After propensity score matching, Kaplan-Meier analysis showed that CIN increased the risk of all-cause deaths, and MACE (Fig. 2).

## DISCUSSION

CIN is a common complication after contrast agent exposure and has an adverse effect on prognosis. Its development has been associated with increased risk of cardiovascular events, morbidity, mortality, and long-term renal impairment.<sup>18-21</sup> At the same time, some known risk factors are closely related to the progression of CIN, and have an extremely important relationship with the short-term prognosis of CIN.

Several risk factors have been confirmed for CIN. CKD, hypotension, diabetes mellitus, volume depletion, neph-

rotoxic medication, hemodynamic instability, and intra-aortic balloon pump usage are all considered to be important risk factors.<sup>15,22-25</sup> For prediction for CIN after PCI, a risk score has been presented by Mehran et al.,<sup>15</sup> including hypotension (5 points), intra-aortic balloon pump (5 points), congestive heart failure (5 points), serum creatinine concentration >1.5 mg/dL (4 points), age >75 years (4 points), anemia (3 points), diabetes mellitus (3 points), contrast volume (1 point for each 100 mL used). The risk score of <6, 6 to 10, 11 to 15, and > 16 mean CIN risks of 7%, 14%, 26%, and 57% respectively.<sup>15,26,27</sup>

However, the risk score did not investigate several factors including hydration volume, urine output, and nephrotoxic medication. Besides, this risk score has only been investigated and established in patients undergoing selective coronary angiography, so it cannot assess the prognosis of primary coronary angiography patients.

In addition based on the above risk factors, the risk factors were adjusted as confounding factors in the data analysis. The confounding factors that are most likely to affect the results of the previous clinical retrospective studies are the baseline renal function levels and whether the hemodynamics are stable. The most direct indicator of renal damage is creatinine. However, creatinine does not fully reflect the level of renal function in patients. Therefore, we added glomerular filtration rate as another indicator of renal function in the study. On the other hand, hemodynamic instability is an important influencing factor of CIN and one of the most important confounding factors in research. In our study, acute coronary syndrome (including STEMI and NSTEMI) was the main manifestation of hemodynamic instability.

Therefore, we used propensity score matching to adjust for confounding factors (including acute myocardial infarction and baseline glomerular filtration rate, etc.). However, after adjusting for confounding factors, CIN was independently associated with long-term risk of 10-year mortality and MACE in the patients who underwent coronary

intervention. That said, even after adjusting the baseline data, the baseline left ventricular ejection fraction was still different. Since there was a relationship between the left ventricular ejection fraction and the development CIN, decreased left ventricular ejection fraction might have an influence on long-term prognosis.<sup>28</sup>

There have been limited studies on the long-term follow-up of CIN. Farhan et al.<sup>29</sup> prospectively followed up 536 patients with acute coronary syndrome (81.6-108.9 months). The incidence of CIN was 9.5% in all study population. However, the patients in the CIN group were older and had higher rates of CKD, anemia, hemofiltration, IABP, and cardiogenic shock.

Giacoppo et al.<sup>2</sup> prospectively followed up with 9,512 patients and observed a CIN rate of 12.7%. Moreover, the mortality rates were significantly higher in the CIN group at 30 days (4.9% vs 0.7%;  $p < 0.0001$ ) and 1 year (9.8% vs 2.9%;  $p < 0.0001$ ). Watabe et al.<sup>30</sup> followed up with 1,059 (means  $435 \pm 330$  days) patients with emergency PCI. The incidence of CIN was 15.9% during the long-term follow-up and the incidence of MACE was higher in the CIN group. These studies showed that patients who developed CIN had increased major cardiovascular risk and a higher mortality rate.

In the general population and special populations (acute coronary syndrome, etc.), the occurrence and short-term adverse prognosis of CIN have been fully investigated. These studies have fully demonstrated the important influence of hemodynamic instability and past renal damage on the occurrence of CIN. On the other hand, there is still a lack of research on the long-term prognosis of CIN. The important reason is that various confounding factors have adversely affected the study results. Therefore, after analyzing the known risk factors, we adjusted the confounding factors that may affect the research results. After using propensity score matching to adjust for baseline confounding factors, CIN still appears to be closely related to poor long-term prognosis. Moreover, CIN was an independent predictor for mortality and MACE. Therefore, in our study, we showed that CIN was associated with poor prognosis during a 10-year clinical follow up.

There are several limitations in our study. First, this is a retrospective single center study. Even after using the data of the Korea National Health Insurance Corporation, there will still be missing follow-ups for some patients after ten-year of follow-up. Second, we used pre-procedural serum creatinine levels as baseline values. The pre-procedural serum creatinine levels may not be the real baseline serum creatinine level because of possible unstable clinical situations. However, our definition of CIN is dependent on serum creatinine, which is an incomplete marker for kidney function. Third, we excluded patients with end-stage renal disease on hemodialysis, but there is sufficient evidence that patients on hemodialysis have a higher risk of adverse cardiovascular events. Fourth, we did not have data on intravenous infusions including nephrotoxic medication, potential renal protection medication, or other con-

trast agent exposure during hospitalization.

In conclusion, there is no clear prevention for CIN other than pre-hydration with saline and reduced dose of contrast media. Our data suggests that it is worthwhile to prevent the appearance of CIN in order to improve long-term results. Future larger studies would be needed to clarify our results.

## CONFLICT OF INTEREST STATEMENT

None declared.

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