Preprocedural High-Sensitivity C-Reactive Protein Predicts Contrast-Induced Nephropathy and Long-Term Outcome After Coronary Angiography

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Abstract
We investigated whether high-sensitivity C-reactive protein (hsCRP) levels were associated with contrast-induced nephropathy (CIN) and long-term mortality after coronary angiography (CAG). Patients (N = 2133) undergoing CAG with preprocedural hsCRP were consecutively enrolled. High-sensitivity C-reactive protein was measured before angiography. Median follow-up was 2.3 years. The overall incidence of CIN was 2.77% (59 of 2133). There was a positive trend of hsCRP quartiles (Q) with rates of CIN: 0.9% for Q1 (<1.6 mg/L), 0.9% for Q2 (1.6-3.9 mg/L), 2.4% for Q3 (4.0-11.3 mg/L), and 6.8% for Q4 (>11.3 mg/L; P < .05). The receiver operating characteristic (ROC) analysis showed that the cutoff point of hsCRP was 7.3 mg/L for predicting CIN with a 72.7% sensitivity and a 67.0% specificity (area under the curve [AUC] = 0.742, 95% confidence interval [CI] 0.672-0.810; P < .05). The predictive value of hsCRP was similar to the Mehran score for CIN (AUC_{hsCRP} = 0.742 vs AUC_{Mehran} = 0.801; P = .228). After adjustment for other potential risk factors, hsCRP >7.3 mg/L still was an independent predictor of CIN (odds ratio [OR] = 2.83, 95% CI: 1.44-5.58; P = .003). Furthermore, hsCRP >7.3 mg/L was associated with higher mortality (OR = 2.04, 95% CI: 1.30-3.19; P = .002).

Keywords
high-sensitivity C-reactive protein, contrast-induced nephropathy, coronary angiography, outcome, Mehran score

Introduction
Contrast-induced nephropathy (CIN) has become more common with the wide use of contrast media (CM).¹ Contrast-induced nephropathy increases in-hospital mortality and dialysis as well as medical burden.² Identifying high-risk patients and early prophylactic measures are important for preventing CIN.³

Mehran et al proposed a risk score including 8 variables to predict CIN after elective percutaneous coronary intervention (PCI).⁴ However, the complexity of the Mehran score limited its application in clinical practice. Therefore, some biomarkers were proposed for the early prediction of CIN and to simplify risk prediction.⁵⁻⁷

High-sensitivity C-reactive protein (hsCRP) is an indicator of systemic inflammation and is related to postprocedural acute kidney injury in high-risk patients.⁸⁻¹² We previously found that hsCRP was a significant and independent predictor for CIN and in-hospital clinical complications in patients with

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We followed the methods used by Liu et al. High-sensitivity hsCRP Protocol This is a prospective observational study conducted at the Guangdong Cardiovascular Institute, Guangdong General Hospital, between January 2010 and October 2012, according to the institutional protocol. The inclusion and exclusion criteria were consistent with the previous study and the Predictive Value of Contrast Volume to Creatinine Clearance Ratio (PRECOMIN, ClinicalTrials.gov; NCT01400295) study. A total of 3273 patients undergoing CAG were consecutively screened in accordance with the updated European Society of Urogenital Radiology Contrast Media Safety Committee guidelines. The exclusion criteria included—(1) lack of preprocedural hsCRP (n = 1099); (2) preprocedural acute infectious diseases including pneumonia, gastrointestinal infection, and urinary tract infection or other concomitant inflammatory condition including inflammatory arthritis, inflammatory bowel disease, or connective tissue disease (n = 25); (3) end-stage kidney disease on dialysis (n = 12); (4) lack of postprocedural serum creatinine (SCr) within 72 hours after CAG (n = 205); (5) allergic to CM (n = 2); and (6) administration of NSAIDs, aminoglycosides, cisplatin, or other nephrotoxic drugs 48 hours before and 72 hours after CAG (n = 35). Finally, 2133 patients undergoing CAG with or without PCI were included in the analysis.

The study was approved by the hospital human research ethics committee and all participants provided informed consent.

Methods

Patients

This is a prospective observational study conducted at the Guangdong Cardiovascular Institute, Guangdong General Hospital, between January 2010 and October 2012, according to the institutional protocol. The inclusion and exclusion criteria were consistent with the previous study and the Predictive Value of Contrast Volume to Creatinine Clearance Ratio (PRECOMIN, ClinicalTrials.gov; NCT01400295) study. A total of 3273 patients undergoing CAG were consecutively screened in accordance with the updated European Society of Urogenital Radiology Contrast Media Safety Committee guidelines. The exclusion criteria included—(1) lack of preprocedural hsCRP (n = 1099); (2) preprocedural acute infectious diseases including pneumonia, gastrointestinal infection, and urinary tract infection or other concomitant inflammatory condition including inflammatory arthritis, inflammatory bowel disease, or connective tissue disease (n = 25); (3) end-stage kidney disease on dialysis (n = 12); (4) lack of postprocedural serum creatinine (SCr) within 72 hours after CAG (n = 205); (5) allergic to CM (n = 2); and (6) administration of NSAIDs, aminoglycosides, cisplatin, or other nephrotoxic drugs 48 hours before and 72 hours after CAG (n = 35). Finally, 2133 patients undergoing CAG with or without PCI were included in the analysis.

The study was approved by the hospital human research ethics committee and all participants provided informed consent.

Protocol

We followed the methods used by Liu et al. High-sensitivity CRP was tested with the Beckman Coulter Image immunobiocommetry system (Boston, Massachusetts, USA) using nephelometer (lowest detection: 0.1 mg/L). Routine blood tests, SCr, and electrolytes were assessed in all participants before the procedure. Coronary angiography and/or stent implantation were performed by a standard clinical technique. All patients received 100 U/kg heparin before angiography with activated partial thromboplastin time monitored during the procedure. The type and volume of CM, intra-aortic balloon pump (IABP), and IIb/IIIa receptor antagonist were left to the discretion of interventional cardiologists and the severity of coronary lesions. All patients were given an intravenous hydration at a rate of 1 mL/kg/h for 2 to 12 hours after CAG. The rate was reduced to 0.5 mL/kg/h if patients had overt heart failure or left ventricular dysfunction (ejection fraction <35%). All patients were prescribed aspirin, clopidogrel, and statins before and after CAG unless contraindicated. Other periprocedural (1 day before and 3 days after CAG) medications were decided by the physician in charge of the patient.

End Points and Definitions

Contrast-induced nephropathy, the primary end point, was defined as an increase in SCr >0.5 mg/dL (44.2 μmol/L) within 72 hours after CAG. The CINeGFR was another definition of CIN as a reduction in estimated glomerular filtration rate (eGFR) >25% within 72 hours after CAG.

The eGFR was evaluated using the modified modification of diet in renal disease equation: 186.3 × SCr−1.154 × (age in years)−0.203 × 1.212 (if patient was black) × 0.742 (if patient was female).

Anemia was defined as hematocrit (HCT) <0.39 (male) or <0.36 (female).

Patients who were diagnosed with STEMI undergoing PCI within 12 to 24 hours after symptom onset were defined as emergency PCI.

Statistical Analysis

All data were analyzed with SAS version 9.2 (SAS Institute, Cary, North Carolina). We compared the baseline characteristics among 4 groups divided by hsCRP quartiles. Normally distributed continuous variables are expressed as mean ± standard deviation (SD) and analyzed with 1-way analysis of variance. Nonnormally distributed variables are expressed as median and interquartile range and analyzed by Kruskal-Wallis tests. The categorical variables are presented as percentage and analyzed by the Pearson χ² test or Fisher exact test. The receiver operating characteristic (ROC) curve was used to find the cutoff value of hsCRP and the Mehran score for CIN. The comparison of hsCRP and the Mehran score in predicting CIN was performed by nonparametric tests. Multivariate logistic regression was performed to calculate the odds ratios (OR) for the risk factors of CIN and CINeGFR. The association of hsCRP with long-term mortality was investigated by Cox regression analysis, and the Kaplan-Meier curve was used to assess the survival time among 4 groups divided by hsCRP quartiles with log-rank test. A 2-sided P value <.05 was considered significant.

Results

Baseline Characteristics

A total of 2133 patients were included in our study. The overall incidence of CIN and CINeGFR were 2.77% (59 of 2133) and 5.21% (111 of 2131), respectively. The average age was 63.3 ± 10.8 years and 505 (23.7%) were female. The mean baseline eGFR was 81.8 ± 25.1 mL/min/1.73 m². Of the total population, 709 (33.6%) had anemia and 310 (14.6%) had preprocedural congestive heart failure.
Cardiac infarction, acute heart failure, and dialysis. and more in-hospital complications including recurrent myo-
hsCRP were related to higher in-hospital mortality (0.2
0.2
An hsCRP cutoff point of 7.3 mg/L predicted by the ROC
ROC Curve
High-Sensitivity C-Reactive Protein Level Predicts CIN by
higher incidence of CIN (0.9
0.9
Table 2 shows that higher hsCRP levels were associated with
more likely to be male and smoker, had higher percentage of
Table 1 shows the clinical and biochemical parameters in
patients from Q1 to Q4 based on the quartiles of preprocedural
hsCRP (Q1: <1.6 mg/L, Q2: 1.6-3.9 mg/L, Q3: 4.0-11.3 mg/L,
and Q4: >11.3 mg/L). Patients with the highest hsCRP were
more likely to be male and smoker, had higher percentage of
chronic heart failure, and had lower baseline eGFR. Patients in
the highest hsCRP group had lower left ventricular ejection fraction (LVEF) and HCT, higher low density lipoprotein cholesterol (LDL-C), more coronary lesions and stents, more CM administered, and higher Mehran CIN score. The periprocedural medications including statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) were not significantly different among the 4 groups.

High-Sensitivity C-Reactive Protein Quartiles With CIN and In-Hospital Outcome
Table 2 shows that higher hsCRP levels were associated with higher incidence of CIN (0.9% vs 0.9% vs 2.4% vs 6.8%, from Q1 to Q4, respectively, P < .001). Furthermore, higher levels of hsCRP were related to higher in-hospital mortality (0.2% vs 0.2% vs 0.4% vs 3.6%, from Q1 to Q4, respectively, P < .001) and more in-hospital complications including recurrent myocardial infarction, acute heart failure, and dialysis.

High-Sensitivity C-Reactive Protein Level Predicts CIN by ROC Curve
An hsCRP cutoff point of 7.3 mg/L predicted by the ROC curve had a sensitivity of 72.7% and a specificity of 67%

Table 1. Baseline Characteristics Among the 4 Groups Divided by hsCRP Quartiles (Q).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Q1 (n = 534)</th>
<th>Q2 (n = 533)</th>
<th>Q3 (n = 536)</th>
<th>Q4 (n = 530)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>133 (24.9)</td>
<td>147 (27.6)</td>
<td>137 (25.6)</td>
<td>88 (16.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>62.3 ± 10.0</td>
<td>63.5 ± 10.7</td>
<td>63.8 ± 10.9</td>
<td>63.6 ± 11.6</td>
<td>.119</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>64.4 ± 10.8</td>
<td>64.7 ± 10.7</td>
<td>64.3 ± 11.3</td>
<td>65.6 ± 10.4</td>
<td>.156</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>172 (32.2)</td>
<td>194 (36.4)</td>
<td>239 (44.6)</td>
<td>265 (50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>310 (58.1)</td>
<td>315 (59.1)</td>
<td>314 (58.6)</td>
<td>306 (57.7)</td>
<td>.971</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>125 (23.4)</td>
<td>133 (25.0)</td>
<td>135 (25.2)</td>
<td>128 (24.2)</td>
<td>.895</td>
</tr>
<tr>
<td>CHF, n (%)</td>
<td>31 (5.9)</td>
<td>51 (9.7)</td>
<td>85 (16.0)</td>
<td>143 (27.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>5 (0.9)</td>
<td>6 (1.1)</td>
<td>4 (0.7)</td>
<td>5 (0.8)</td>
<td>.9</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>86.4 ± 23.0</td>
<td>83.0 ± 24.0</td>
<td>81.35 ± 25.0</td>
<td>76.7 ± 27.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>0.79 ± 0.40</td>
<td>2.55 ± 0.67</td>
<td>6.77 ± 2.02</td>
<td>39.73 ± 36.20</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>61.6 ± 11.0</td>
<td>60.0 ± 11.7</td>
<td>58.1 ± 12.9</td>
<td>54.2 ± 13.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.4 ± 0.8</td>
<td>2.6 ± 1.0</td>
<td>2.7 ± 0.9</td>
<td>2.7 ± 1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coronary lesions</td>
<td>1.7 ± 1.2</td>
<td>1.9 ± 1.2</td>
<td>2.1 ± 1.1</td>
<td>2.3 ± 1.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number of stent</td>
<td>1.4 ± 1.3</td>
<td>1.5 ± 1.3</td>
<td>1.9 ± 4.7</td>
<td>1.7 ± 1.2</td>
<td>.004</td>
</tr>
<tr>
<td>Length of stent, mm</td>
<td>34.3 ± 33.8</td>
<td>36.95 ± 33.2</td>
<td>39.5 ± 33.7</td>
<td>43.1 ± 31.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Contrast volume, mL</td>
<td>116.7 ± 68.1</td>
<td>126.6 ± 71.4</td>
<td>130.4 ± 66.9</td>
<td>138.0 ± 62.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mehran CIN score</td>
<td>3.85 ± 3.10</td>
<td>4.34 ± 3.41</td>
<td>5.05 ± 3.92</td>
<td>6.16 ± 4.51</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Periprocedural IABP</td>
<td>3 (0.6%)</td>
<td>4 (0.8%)</td>
<td>11 (2.1%)</td>
<td>39 (7.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Preprocedural hypotension</td>
<td>4 (0.8%)</td>
<td>5 (0.9%)</td>
<td>5 (0.9%)</td>
<td>16 (3.0%)</td>
<td>.004</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>514 (96.3)</td>
<td>514 (96.3)</td>
<td>514 (96.3)</td>
<td>514 (96.3)</td>
<td>.959</td>
</tr>
<tr>
<td>ACEI/ARB, n (%)</td>
<td>478 (89.5)</td>
<td>475 (89.1)</td>
<td>478 (89.2)</td>
<td>459 (86.6)</td>
<td>.415</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CABG, coronary artery bypass grafting; CHF, chronic heart failure; CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; IABP, intra-aortic balloon pump; LDL-C, low-intensity lipoprotein cholesterol; LVEF, left ventricular ejection fraction.

Table 2. High-Sensitivity C-Reactive Protein Quartiles (Q) With CIN and In-Hospital Outcome.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Q1 (n = 534)</th>
<th>Q2 (n = 530)</th>
<th>Q3 (n = 536)</th>
<th>Q4 (n = 530)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN</td>
<td>5 (0.9%)</td>
<td>5 (0.9%)</td>
<td>13 (2.4%)</td>
<td>36 (6.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recurrent MI</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
<td>6 (1.1%)</td>
<td>.004</td>
</tr>
<tr>
<td>AHF</td>
<td>2 (0.4%)</td>
<td>5 (0.9%)</td>
<td>4 (0.7%)</td>
<td>26 (4.9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>2 (0.4%)</td>
<td>9 (1.7%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: AHF, acute heart failure; CIN, contrast-induced nephropathy; MI, myocardial infarction.

High-Sensitivity C-Reactive Protein Level Predicts CIN by ROC Curve
An hsCRP cutoff point of 7.3 mg/L predicted by the ROC curve had a sensitivity of 72.7% and a specificity of 67%

Risk Factors of CIN and CIN[eGFR] by Multivariate Logistic Regression
According to the ROC cutoff point (7.3 mg/L), we divided the population into hsCRP >7.3 mg/L and hsCRP ≤7.3 mg/L. High-sensitivity C-reactive protein >7.3 mg/L was a predictor for CIN in univariate logistic regression (OR: 4.90, 95% CI: 2.76-8.69; P < .001). Multivariate logistic regression found that hsCRP >7.3 mg/L was still an independent predictor for CIN (OR: 2.83, 95% CI: 1.44-5.58; P = .003), after adjusting for the other established risk factors, including statin use, IABP,
eGFR, age >75 years, anemia, LVEF <35%, and coronary lesions (Table 3).

The multivariable logistic analysis of CINeGFR showed that higher hsCRP (>7.3 mg/L) is an independent risk factor for CINeGFR (OR: 1.54, 95% CI: 1.01-2.35, P = .046), after adjusting for confounders, including age >75 years, anemia, IABP, LVEF <35%, statin use, and coronary lesions (Table 4).

**Table 3. Univariate and Multivariate Logistic Analysis for CIN.**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Univariate Logistic Analysis</th>
<th>Multivariate Logistic Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.95</td>
<td>1.15-3.30</td>
</tr>
<tr>
<td>hsCRP &gt;7.3 mg/L</td>
<td>4.90</td>
<td>2.76-8.69</td>
</tr>
<tr>
<td>IABP</td>
<td>16.88</td>
<td>8.70-32.73</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.95</td>
<td>0.94-0.96</td>
</tr>
<tr>
<td>LVEF &lt;35%</td>
<td>2.21</td>
<td>1.09-4.47</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>4.86</td>
<td>2.84-8.33</td>
</tr>
<tr>
<td>Coronary lesion</td>
<td>1.34</td>
<td>1.13-1.58</td>
</tr>
<tr>
<td>Statins use</td>
<td>0.36</td>
<td>0.15-0.85</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; OR, odds ratio.

**Table 4. Multivariate Logistic Analysis for CINeGFR.**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Multivariate Logistic Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>hsCRP &gt;7.3 mg/L</td>
<td>1.54</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.00</td>
</tr>
<tr>
<td>IABP</td>
<td>0.45</td>
</tr>
<tr>
<td>LVEF &lt;35%</td>
<td>1.62</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>1.97</td>
</tr>
<tr>
<td>Coronary lesion</td>
<td>1.05</td>
</tr>
<tr>
<td>Statins use</td>
<td>4.03</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; OR, odds ratio.

**High-Sensitivity C-Reactive Protein Predicts Long-Term Mortality by Survival Analysis**

The median follow-up period was 2.3 years. Cox regression analysis revealed that hsCRP was an independent risk factor for long-term mortality (OR: 2.04, 95% CI: 1.30-3.19, P = .002) after adjusting for other risk factors including age >75 years, female, anemia, DM, IABP, emergency PCI, hypotension, and eGFR (Figure 2). The Kaplan-Meier curve showed that group Q4 demonstrated the highest mortality and the least survival time compared to the other 3 groups (log-rank, P < .001; Figure 3).

**Discussion**

Our study suggests hsCRP >7.3 mg/L is an independent risk factor for CIN in patients undergoing CAG. Furthermore, hsCRP was similar to the Mehran score in predicting CIN in this unselected population. The HsCRP was a strong indicator for long-term mortality after CAG and could be useful for risk stratification.

We used 2 definitions of CIN (increase in SCr and reduction in eGFR). The 2011 CIN guideline stated that a further suggestion for a threshold for the diagnosis of CIN is a 25% decrease from baseline eGFR.14 However, eGFR reduction did not reflect the sensitive change in renal function in patients with normal baseline eGFR. Most patients had normal renal function in our study; the mean baseline eGFR was 81.8 ±
25.1 mL/min/1.73 m². The accuracy of using eGFR reduction as CIN definition with normal renal function has not been validated. Furthermore, most articles applied the increase in SCr (>0.5 mg/dL and/or 25%) within 72 hours after CM exposure as the definition of CIN. So, we used SCr elevation rather than eGFR reduction in order to be consistent with other studies. Previous studies reported an incidence of CIN as 3% to 20% that was higher than that in our study. The restricted definition of CIN (>0.5 mg/dL) contributed to the low incidence of CIN in our study. And those studies enrolled patients with ACS or undergoing PCI, whereas our study enrolled those undergoing CAG, including some low-risk patients. Some low-risk patients who received a rather low dose of CM (<50 mL) without stent implantation demonstrated reversible renal function, even so they reached the threshold of CIN. We have found hsCRP performed well in discriminating CIN in high-risk patients undergoing primary PCI and the predicting ability of hsCRP was reflected in both low-risk patients and high-risk patients in our series studies. Patients undergoing only CAG may not receive a sufficient hydration strategy for preventing CIN in clinical practice. But effective prophylactic measures can be taken in time if such patients had an elevated hsCRP that indicates high risk of CIN before CAG.

A number of studies show hsCRP is a strong predictor for CIN. The results of our study are consistent with our previous study of 165 patients with STEMI with primary PCI. We found CRP level >16.1 mg/L was related to the incidence of CIN and in-hospital complications. The previous study focused on high-risk patients with emergency PCI and an incidence of CIN of 10%. The present study found that hsCRP performed well in predicting CIN (2.77%) in low-risk patients, even in unselected patients undergoing CAG. Gao et al enrolled 4522 patients undergoing PCI and divided the population into 3 groups according to the preprocedural C-reactive protein (CRP) values (group 1: CRP <1.0 mg/L; group 2: 1.0 mg/L ≤ CRP ≤ 3.0 mg/L; and group 3: CRP >3.0 mg/L). They found that the preprocedural CRP level was associated with contrast-induced acute kidney injury and all-cause mortality during long-term follow-up. The results were similar to those of our study but included those with PCI who were given more contrast volume and might suffer worse cardiac function. This might indicate hsCRP level could distinguish those CIN high-risk patients. Our study demonstrated a different hsCRP cutoff point (7.3 mg/L) compared to previous studies probably because of the different inclusion criteria and CIN definition.

Recently, a number of clinical trials and meta-analyses have suggested that periprocedural statin treatment can prevent CIN and improve long-term outcomes in both high-risk and low-risk patients. The protecting value of statins might involve lowering the level of hsCRP. Statin treatment has the potential benefit on proteinuria and preserving renal function in chronic kidney disease, which prevent cardiovascular disease from worsening.

Several risk models have been applied to predict CIN in clinical practice. Mehran et al enrolled 8357 participants with elective PCI and proposed the Mehran score including 8 variables (hypotension, congestive heart failure, diabetes, chronic kidney disease, elderly, anemia, IABP, and contrast medium volume). The risk model was also effective in distinguishing CIN after emergency PCI. But the Mehran score was not widely used in clinical practice because some variables such as IABP and CM medium volume are not available before CAG. High-sensitivity C-reactive protein levels are easily obtained before coronary intervention and the results are reliable and repeatable. Our study demonstrated that hsCRP had a similar predictive value to the Mehran score for CIN. High-sensitivity C-reactive protein is much more convenient and easily available than the Mehran score in clinical practice. It is promising for rapid screening of CIN, facilitating timely preventive intervention.

Inflammatory factors play an important role in the process of CIN. First, higher levels of hsCRP are associated with endothelial dysfunction that leads to vascular impairment, decreasing renal blood flow, and exacerbating renal function. Second, overexpression of oxidative reaction and reduction in nitric oxide production are related to elevated hsCRP and contribute to the development of CIN. Such mechanisms may explain why elevated hsCRP levels predicted CIN in this study.

Similarly, our study suggested the predictive value of hsCRP for long-term outcome (median 2.3-year follow-up). We found that being elderly participants and undergoing emergency PCI were other 2 risk factors associated with worse outcome, whereas common risk factors of CIN such as IABP, anemia, hypotension, and chronic kidney disease were not. Anemia, chronic kidney disease, and chronic heart failure are
known predictors of CIN from previous studies.\textsuperscript{32,33} We inferred that hsCRP was associated with CIN through those risk factors. Recently, Abaci et al reported contrast exposure was a risk factor for poor long-term outcome independent of CIN in high-risk patients.\textsuperscript{34} A meta-analysis even concluded that patients exposed to CM demonstrated a similar incidence of acute kidney injury compared to those who were not exposed.\textsuperscript{35} However, CIN was still confirmed as associated with worse outcome and several strategies were compared for preventing CIN in order to improve outcome.\textsuperscript{36} The association between CIN and long-term outcome was confounded by some baseline characteristics. Being elderly participants having chronic renal dysfunction and elevated hsCRP was the common risk factor of both CIN and long-term mortality in the present study.\textsuperscript{37} The potential mechanism may be related to the interaction between hsCRP and risk factors above. Poor cardiac function and severe coronary lesions that need hemodynamic support are common risk factors that are associated with poor outcome in patients with acute renal failure undergoing cardiac intervention.\textsuperscript{38} However, multi-vessel disease, LVEF <35\%, and IABP were not significantly associated with poor prognosis in our study which needs further exploration.

**Limitations**

This study has several limitations. First, baseline characteristics among the 4 groups were not well matched partially because some characteristics were related to the hsCRP level. Thus, multivariate analysis of CIN and Cox-regression analysis of outcome were influenced by the unmatched bias. Second, we lacked postprocedural hsCRP results that could help to monitor the change of inflammatory response after exposure to CM. Third, due to the restricted definition, the rate of CIN was low that might reduce the accuracy and reliability of the CIN multivariate model. Thus, we need a large-scale prospective study with well-matched risk factors and continuously monitored hsCRP to prove our conclusion.

**Conclusion**

Our findings corroborate the view that preprocedural hsCRP levels are an independent marker for predicting CIN and long-term mortality in unselective patients undergoing CAG. The predicting value of hsCRP, as simple tool, is similar to the Mehran score for risk stratification of CIN. However, the association needs to be verified by a large-scale prospective study.

**Authors' Note**

Xiao-sheng Guo, Kai-yang Lin, and Hua-long Li contributed equally to this work.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by a grant from the Guangdong Provincial Cardiovascular Clinical Medicine Research Fund (grant no. 2009X41; Yong Liu and Ning Tan), Science and Technology Planning Project of Guangdong Province (PRECOMIN study; Yong Liu in 2011 and study grant no. 2008A030201002; Ji-Yan Chen), and Guangdong Cardiovascular Institute.

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