**Original Article**

**Serum cystatin C and creatinine levels could predict the outcome of contrast-induced nephropathy after percutaneous coronary intervention: a meta-analysis of 1153 patients from 11 studies**

Yu-Rui Duan¹*, Yang Li²*, Bao-Ping Chen¹, Xiao-Dong Li², Chao-Yang Zhu²

Departments of ¹Nephrology, ²Urinary Surgery Second Ward, Huaiehe Hospital, Henan University, Kaifeng 475000, P. R. China. *Co-first authors.

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**Abstract:** Objective: The present meta-analysis investigates the clinical value of two contrast-induced nephropathy (CIN) markers, serum cystatin C and creatinine, for their application as prognostic markers in percutaneous coronary intervention (PCI). Methods: The relevant scientific literature research databases were retrieved according to strict inclusion and exclusion criteria, and the selected studies were further screened for our meta-analysis. Statistical analysis of the extracted data was performed using Comprehensive Meta-analysis 2.0 (CMA 2.0) software. Results: We initially retrieved 1702 published studies and found 11 studies eligible for the current meta-analysis. The 11 selected studies contained a total of 1153 CIN patients. The results of our meta-analyses showed that serum cystatin C and creatinine levels were significantly lower in CIN patients after PCI therapy compared to those before PCI therapy (Cystatin C: SMD = -1.713, 95% CI = -2.479~−0.946, P < 0.001; Creatinine: SMD = -0.499, 95% CI = -0.856~−0.142, P = 0.006). In support of their clinical value to PCI, the estimated glomerular filtration rate (eGFR) was not significantly different in CIN patients before and after PCI therapy (SMD = -0.036, 95% CI = -0.499~0.427, P = 0.879). Ethnicity-based subgroup analysis clarified that serum cystatin C levels were significantly lower in CIN patients after PCI therapy, in comparison to before PCI therapy, in Asians (SMD = -2.196, 95% CI = -3.262~−1.131, P < 0.001), but such correlation was not observed in Caucasians (SMD = -0.574, 95% CI = -1.170~0.022, P = 0.059). Conclusion: Our study findings strongly support that serum cystatin C and creatinine levels can predict the success of PCI in Asian CIN patients, and PCI has no significant influence on eGFR.

**Keywords:** Percutaneous coronary intervention, contrast-induced nephropathy, contrast associated nephropathy, cystatin C, creatinine, eGFR, prognosis, meta-analysis

**Introduction**

Contrast-induced nephropathy (CIN), also known as contrast-induced acute kidney injury (AKI), is a feared complication related to intra-vascular administration of radio contrast media [1, 2]. It is the third most common cause of deterioration of in-hospital renal function, and the morbidity of CIN in the common population is estimated at 1~2% [3, 4]. Although the condition is mostly benign and idiopathic, its mortality rates vary depending on the clinical setting [5, 6]. Previous studies showed that the incidence of CIN was as low as 2% among low risk patients and is significantly elevated at 50% in high-risk patients, and the incidence of CIN is projected to increase in the coming years [7, 8]. The risk factors of CIN are either patient-related or procedure-related, and include increased S-creatinine levels, advanced age, dehydration, congestive heart failure, concurrent administration of nephrotoxic drugs, secondary to diabetic nephropathy, and high dose of contrast medium (CM) and high osmolar contrast media [9, 10]. The pathophysiology of CIN is multi-factorial and is correlated with perturbations in glomerular flow, adenosine, prostaglandin and endothelial metabolism, and oxidative stress [11, 12]. Treatments for CIN involve administration of N-acetylcysteine (NAC), statins, theoph-
Prognostic effect of CIN undergoing PCI

Percutaneous coronary intervention (PCI), commonly known as coronary angioplasty, is a non-invasive procedure to relieve occlusion or large risk of occlusion in a coronary artery, usually in a single-vessel disease condition [15]. In this type of intervention, the culprit vessel is identified within 12 hours after the onset of chest pain, without using clot-dissolving treatment or other previous thrombolytic therapies [16]. It was administered to only single-vessel disease patients when PCI was first introduced in 1977, but with advances in device technologies, PCI can be applied to treat patients with complex diseases, such as left main coronary disease and multi-vessel disease conditions [17]. More than 1.5 million patients undergo PCI each year in the United States [18], and the procedure is performed through a small intra-arterial sheath for balloon inflation to dilate the coronary stenosis, and a stent is implanted to scaffold the dilated portion of the vessel [19]. As technology improved, several PCI methods are routinely used, such as coronary stenting, which contains bare-metal stent (BMS) and drug-eluting stents (DES), preventive angioplasty, and rotational atherectomy [20-22]. Serum cystatin C and creatinine levels are early diagnostic markers of CIN and studies have indicated their prognostic value in CIN, and their serum levels evidently influenced by PCI therapy [23-25]. However, several other studies questioned the clinical value of the serum markers in PCI [26, 27]. To solve this issue, a systematic meta-analysis was conducted to investigate the clinical value of serum cystatin C, creatinine and eGFR levels in patients undergoing PCI.

Materials and methods

Sources of data and keywords

In order to recognize relevant studies, we exhaustively searched PubMed, EBSCO, Ovid, Springerlink, Wiley, Web of Science, Wanfang databases, China National Knowledge Infrastructure (CNKI) databases, VIP databases (last updated search in October, 2014), employing selected common keywords related to PCI and CIN. The retrieval items were: “contrast-induced nephropathy” or “contrast induced nephropathy” or “CIN” or “contrast associated nephropathy” or “CAN” and “percutaneous coronary intervention” or “PCI” or “coronary angiography”. Manual search was also conducted to discern other relevant studies using cross-references of pertinent articles.

Inclusion and exclusion criteria

Published studies selected for the present meta-analysis fulfilled the below inclusion criteria: (1) research type: clinical experimental studies involving PCI therapy in CIN patients; (2) research object: all patients should be clinically diagnosed as CIN; (3) end outcome: the influence of PCI on CIN patients’ cystatin C, creatinine and eGFR. Study exclusion criteria were: (1) only summary or abstracts; (2) animal studies; (3) repeat publication; (4) incomplete data; (5) only the most newly published study for reference when screening the studies from the same authors.

Data extraction and quality assessment

A detailed standard data extraction form was used by two investigators to independently extract data from all selected studies, and...
agreement on all items were reached via discussion. The following data were extracted: first author’s surname, publication time, country, ethnicity, language, age, gender, number of case and controls, study design and intervention study. The qualities of all enrolled studies were evaluated by two investigators independently according to Methodological Index for Non-Randomized Studies (MINORS) criteria (Figure 1) [28], which included 12 detailed items: a specific purpose (MINORS01); consecutive patients (MINORS02); prospective collection of data (MINORS03); endpoints reflect the purpose of the study (MINORS04); unbiased estimate of endpoint (MINORS05); ample follow-up period (MINORS06); loss to follow-up < 5% (MINORS07); prospective evaluation of 95% confidence interval of sample size (MINORS08); a suitable control group (MINORS09); contemporary groups (MINORS10); baseline equivalence of groups (MINORS11); appropriate statistical analyses (MINORS12).

Statistical analysis

Comprehensive Meta-analysis 2.0 software (Biostat Inc., Englewood, USA) was used for meta-analysis. The influence of PCI on CIN patients’ clinical parameters, cystatin C, creatinine and eGFR, was evaluated by standard mean difference (SMD) or odds ratio (OR) and its 95% confidence intervals (95% CI) under a fixed-effects or a random effects model. In addition, Z-test was applied to ascertain the significance of pooled SMDS [29]. The Cochran’s Q-statistic ($P < 0.05$ refers to significant) and $I^2$ test (0% means no heterogeneity; 100% means maximal heterogeneity) were also conducted to show the heterogeneity among studies [30, 31]. Random effects model was utilized in cases of significant heterogeneity ($P < 0.05$ or $I^2$ test exhibited > 50%), otherwise, fixed-effects model was conducted [32]. The univariate and multivariate meta-regression analysis were conducted for finding potential source of heterogeneity was evaluated by univariate and multivariate meta-regression analysis which was further reexamined by Monte Carlo simulation (MCS) [3, 30, 33]. A sensitivity analysis was applied for assessing whether the individual study results had a significant effect on the overall results by deleting a single study one by one. Furthermore, Begger’s funnel plot, classic fail-safe N and Egger test were conducted to assess publication bias to further confirm the original result [34, 35]. All tests were two-sided, and $P$ values < 0.05 were considered statistically significant.

Results

Baseline characteristics of included studies

Relevant studies (1702) were retrieved by the stringent electronic database search and manual search. Subsequently, studies were screened by excluding duplicates ($n = 214$), letters, reviews or meta-analyses ($n = 208$), non-human studies ($n = 549$) and studies not related to our research topic ($n = 128$). The remaining studies ($n = 603$) were reviewed and additional 589 studies were excluded because they did not represent case-control or cohort study ($n = 189$), were not relevant to CIN ($n = 208$), or not

**Table 1.** Baseline characteristics for the 10 eligible studies

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Ethnicity</th>
<th>Country</th>
<th>Study design</th>
<th>Interventions</th>
<th>Patients Number</th>
<th>Gender (M/F)</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bachorzewska-Gajewska H</td>
<td>2007</td>
<td>Caucasians</td>
<td>Poland</td>
<td>Non-RCT</td>
<td>PCI</td>
<td>100</td>
<td>-</td>
<td>63.2 ± 12.0</td>
</tr>
<tr>
<td>Kato K</td>
<td>2008</td>
<td>Asians</td>
<td>Japan</td>
<td>Non-RCT</td>
<td>PCI</td>
<td>87</td>
<td>62/25</td>
<td>67 ± 11</td>
</tr>
<tr>
<td>Rehman T</td>
<td>2008</td>
<td>Caucasians</td>
<td>USA</td>
<td>Non-RCT</td>
<td>PCI</td>
<td>100</td>
<td>59/41</td>
<td>65.3 ± 11.7</td>
</tr>
<tr>
<td>Ishibashi Y</td>
<td>2010</td>
<td>Asians</td>
<td>Japan</td>
<td>Non-RCT</td>
<td>PCI</td>
<td>18</td>
<td>-</td>
<td>68.8 ± 10.0</td>
</tr>
<tr>
<td>Chen HQ</td>
<td>2011</td>
<td>Asians</td>
<td>China</td>
<td>Non-RCT</td>
<td>PCI</td>
<td>84</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ribichini F</td>
<td>2012</td>
<td>Caucasians</td>
<td>Italy</td>
<td>Non-RCT</td>
<td>PCI</td>
<td>30</td>
<td>20/10</td>
<td>75.0 (64.3-79.8)</td>
</tr>
<tr>
<td>Tanaga K</td>
<td>2012</td>
<td>Asians</td>
<td>Japan</td>
<td>Non-RCT</td>
<td>PCI</td>
<td>18</td>
<td>-</td>
<td>61.9 ± 8.2</td>
</tr>
<tr>
<td>Chen ZF</td>
<td>2012</td>
<td>Asians</td>
<td>China</td>
<td>Non-RCT</td>
<td>PCI</td>
<td>100</td>
<td>68/32</td>
<td>56.4 ± 7.2</td>
</tr>
<tr>
<td>Zhao YY</td>
<td>2012</td>
<td>Asians</td>
<td>China</td>
<td>Non-RCT</td>
<td>PCI</td>
<td>472</td>
<td>294/178</td>
<td>55.2 ± 13.0</td>
</tr>
<tr>
<td>Alharazy SM</td>
<td>2014</td>
<td>Asians</td>
<td>Malaysia</td>
<td>Non-RCT</td>
<td>PCI</td>
<td>11</td>
<td>-</td>
<td>60.4 ± 8.3</td>
</tr>
<tr>
<td>Pan FJ</td>
<td>2014</td>
<td>Asians</td>
<td>China</td>
<td>Non-RCT</td>
<td>PCI</td>
<td>133</td>
<td>77/56</td>
<td>56.37 ± 20.49</td>
</tr>
</tbody>
</table>

Non-RCT: Non-randomized controlled trial; PCI: Percutaneous coronary intervention; M: Male; F: Female.
relevant to PCI (n = 192). After further assessment, 3 studies were removed for not containing sufficient information. Finally, 11 eligible studies, published between 2007 and 2014, were selected for meta-analysis, and included a total of 1,153 CIN patients (sample size: 11~472) [23, 26, 27, 36-43]. Of the 11 studies, a total of 3 studies were performed in Caucasians (1 from Poland, 1 from USA and 1 from Italy), and 8 studies were in Asians (3 from Japan, 4 from China and 1 from Malaysia). Baseline characteristics of all the enrolled relevant studies are shown in Table 1.

**Pooled outcome of meta-analysis**

The influence of PCI in CIN patients’ serum cystatin C level: All eleven studies reported the influence of PCI on serum cystatin C levels in CIN patients. Random effect model was applied.

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**Figure 2.** Forest plots of the influence of percutaneous coronary intervention in contrast-induced nephropathy patients’ serum cystatin C, creatinine level and eGFR (Std diff: standard difference).
Prognostic effect of CIN undergoing PCI

due to heterogeneity among studies ($I^2 = 98.208\%$, $P < 0.001$). The result of our meta-analysis showed that serum cystatin C level in CIN patients after PCI therapy was significantly lower than that before PCI treatment (SMD = -2.196, 95% CI = -3.262--1.131, $P < 0.001$), but not among Caucasians (SMD = -0.574, 95% CI = -1.170--0.022, $P = 0.059$) (Figure 3A).

The influence of PCI in CIN patients’ serum creatinine level: All eleven studies also clarified the influence of PCI on serum creatinine level in CIN patients. Due to heterogeneity among studies ($I^2 = 92.998\%$, $P < 0.001$), random effects

Figure 3. Forest plots of the influence of percutaneous coronary intervention in contrast-induced nephropathy patients’ serum cystatin C, creatinine level and eGFR in subgroup analyses by ethnicity (Std diff: standard difference).
model was employed. Our meta-analysis showed that serum creatinine level of CIN patients after PCI therapy was significantly lower than that before PCI therapy (SMD = -0.499, 95% CI = -0.856~ -0.142, \( P = 0.006 \)) (Figure 2B). Ethnicity-based subgroup analysis clarified that
Prognostic effect of CIN undergoing PCI

Figure 5. Publication biases of the influence of percutaneous coronary intervention in contrast-induced nephropathy patients’ serum cystatin C, creatinine level and eGFR.

serum creatinine level of CIN patients after PCI therapy was significantly lower than before PCI therapy among Asians (SMD = -0.450, 95% CI = -0.850~ -0.051, P = 0.027), but such significant
Prognostic effect of CIN undergoing PCI

A
Cystatin C
Regression of Year on Std diff in means
P = 0.367
Adj R-squared = -1.93%

B
Cystatin C
Regression of ethnicity on Std diff in means
P = 0.517
Adj R-squared = -6.15%

C
Cystatin C
Regression of country on Std diff in means
P = 0.546
Adj R-squared = -6.79%

D
Cystatin C
Regression of language on Std diff in means
P = 0.111
Adj R-squared = 17.51%

E
Creatinine
Regression of Year on Std diff in means
P = 0.452
Adj R-squared = -3.60%

F
Creatinine
Regression of ethnicity on Std diff in means
P = 0.674
Adj R-squared = -11.91%

G
Creatinine
Regression of country on Std diff in means
P = 0.302
Adj R-squared = -4.32%

H
Creatinine
Regression of language on Std diff in means
P = 0.737
Adj R-squared = -11.20%

I
eGFR
Regression of Year on Std diff in means
P = 0.819
Adj R-squared = -68.02%

J
eGFR
Regression of ethnicity on Std diff in means
P = 0.875
Adj R-squared = -82.46%

K
eGFR
Regression of country on Std diff in means
P = 0.987
Adj R-squared = -34.68%

L
eGFR
Regression of language on Std diff in means
P = 0.417
Adj R-squared = -1.12%
correlations were not detected among Caucasians (SMD = -0.691, 95% CI = -1.670~0.289, \(P = 0.167\)) (Figure 3B).

The influence of PCI in CIN patients’ eGFR: Four studies documented the influence of PCI on eGFR of CIN patients. Random-effects model was employed due to heterogeneity among these studies (\(I^2 = 76.594\%\), \(P_h = 0.005\)). The results of our meta-analysis showed no statistically significant differences in eGFR between CIN patients after PCI therapy (SMD = -0.036, 95% CI = -0.499~0.427, \(P = 0.879\)) (Figure 2C). Subgroup analysis on the basis of ethnicity demonstrated that eGFR in CIN patients before and after PCI also showed no significant differences in both Asian and Caucasian populations (Asians: SMD = -0.114, 95% CI = -0.969~0.742, \(P = 0.794\); Caucasians: SMD = 0.030, 95% CI = -0.247~0.307, \(P = 0.831\)) (Figure 3C).

Sensitivity analysis and publication bias

Sensitivity analysis showed that all selected relevant studies had no detectable influence on the pooled SMD on the clinical efficacy of PCI in CIN (Figure 4). No publication bias existed, as evidenced by symmetrical funnel plots, and classic fail-safe N and Egger’s linear regression test further confirmed the result (\(P > 0.05\)) (Figure 5). Univariate and multivariate meta-regression analysis showed that publication year, ethnicity, country, and language were not the sources of heterogeneity or the crucial factors that influenced overall effect size (all \(P > 0.05\)) (Figure 6; Table 2).

### Discussion

In our meta-analysis, we investigated the influence of PCI in CIN, with particular interest in three clinical diagnostic parameters. The final result of our meta-analysis clearly showed that serum cystatin C and creatinine level in CIN patients were significantly lower after PCI therapy, compared to before PCI treatment, while no significant changes were observed in the eGFR of CIN patients before and after PCI therapy. The rise in absolute values of serum creatinine (Cr) \(\geq 0.5\) mg/dL within 48-72 hours after iodinated contrast medium administration or a 25% increase from baseline serum creatinine levels, within 48-72 hours after administration of iodinated contrast medium, are the clinical standards in CIN diagnosis [44-46]. CIN is an iatrogenic disease, mainly caused by adverse response to iodinated contrast media, during diagnostic or therapy procedures for various diseases [47]. PCI is also extensively employed to non-invasively treat many diseases, including ST-elevation myocardial infarction, acute coronary syndrome and complex disease such as left main coronary disease and multi-vessel disease [48, 49]. PCI therapy includes a deflat-
Prognostic effect of CIN undergoing PCI

ed balloon, or other devices used by cardiologists, to pass through blood vessels until they reach the correct site of blockage in the heart, and subsequently the balloon is inflated to relieve the blockage to allow blood flow [50]. PCI has several benefits that improves patient outcome because it is guided by a relatively minimally invasive assessment of coronary stenoses and can provide immediate symptom relief [51, 52]. One previous study showed that PCI therapy actually significantly increased the two early markers for CIN, serum cystatin C and creatinine, and also elevated neutrophil gelatinase-associated lipocalin (NGAL) after PCI therapy within 4-24 hrs [25]. Our present meta-analysis results are directly in contrast to these results. In our study, both serum cystatin C and creatinine levels were markedly reduced after PCI therapy. The use of contrast media during PCI may lead to diuresis and natriuresis which can cause the decrease of adenosine, leading to the vasoconstriction of the afferent arteriole of the glomerulus and the medullary vascular bed [46]. Especially, contrast exposure may result in medullar densa, releasing angiotensin, vasopressin and endothelin, as well as the decrease of synthesis of nitric oxide, and other organ injury may occur including oxidative stress, interstitial inflammation, and endothelial dysfunction [53]. Nevertheless, the decreases we observed in serum cystatin C and creatinine levels, using data extracted from previous studies, will need to be examined closer to better understand the clinical features of patients who showed such decreases.

In order to evaluate other factors affecting the validity of our overall results, the current meta-analysis conducted a subgroup analysis based on ethnicity. The result of our subgroup analysis showed that serum cystatin C and creatinine level of CIN patients after PCI treatment were significantly lower than before PCI treatment among Asians, but we did not find this statistically significant among Caucasians. Interestingly, eGFR in CIN patients before and after PCI therapy showed no statistically significant differences in Asian and Caucasian populations.

Similar to other published meta-analysis, we acknowledged limitations in our meta-analysis. First, number of enrolled studies was comparatively small, which might lead to the lack of confidence in the overall results. Second, the absence of some data in end-outcome may result in the lower confidence in the validity of our results. Third, language bias might exist in this study because literature published in languages other than English and Chinese were excluded in our meta-analysis.

In conclusion, our meta-analysis provides evidence that PCI therapy can reduce the serum cystatin C and creatinine levels, and PCI has no significant effect on eGFR in CIN patients. However, further studies using larger sample size are needed to confirm the present results.

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Disclosure of conflict of interest

None.

Address correspondence to: Chao-Yang Zhu, Department of Urinary Surgery Second Ward, Huaihe Hospital, Henan University, Baobei Road No. 8, Kaifeng 475000, Henan Province, P. R. China. Tel: +86-378-23906692; E-mail: chaoyang1116@163.com

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Prognostic effect of CIN undergoing PCI


Prognostic effect of CIN undergoing PCI


