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 Duan[1*], Yang Li[2*], Bao-Ping Chen[1], Xiao-Dong Li[2], Chao-Yang Zhu[2]

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

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 intravascular 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-

Figure 1. The quality of a sum of eleven enrolled studies in our meta-analysis was evaluated by Methodological Index for Non-Randomized Studies criteria.

ylline, sodium bicarbonate, and interventional therapy [13, 14].

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

Table 1. Baseline characteristics for the 10 eligible studies

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

Non-RCT: Non-randomized controlled trail; PCI: Percutaneous coronary intervention; M: Male; F: Female.

agreement on all items were reached via discussion. The following data were extracted: first author' 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

A

Cystatin C
(Preoperative VS. Postoperative)

Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Std diff in means and 95%CI	Relative weight	Std Residual
Bachorzewska-Gajewska H (2007)	-0.422	0.143	0.020	-0.703	-0.142	-2.953	0.003		9.47	1.07
Kato K (2008)	-0.117	0.152	0.023	-0.414	0.181	-0.770	0.441		9.46	1.32
Rehman T (2008)	-0.061	0.141	0.020	-0.338	0.216	-0.432	0.666		9.48	1.37
Ishibashi Y (2010)	-0.248	0.335	0.112	-0.903	0.408	-0.740	0.459		8.97	1.18
Chen HQ (2011)	-0.362	0.156	0.024	-0.667	-0.057	-2.328	0.020		9.45	1.12
Ribichini F (2012)	-1.400	0.288	0.083	-1.965	-0.835	-4.859	0.000		9.12	0.25
Tanaga K (2012)	-1.067	0.356	0.127	-1.765	-0.369	-2.995	0.003		8.89	0.52
Chen ZF (2012)	-12.716	0.651	0.424	-13.993	-11.440	-19.523	0.000		7.58	-8.06
Zhao YY (2012)	-1.227	0.071	0.005	-1.366	-1.088	-17.294	0.000		9.57	0.40
Alharazy SM (2014)	-0.425	0.431	0.186	-1.270	0.420	-0.986	0.324		8.59	1.01
Pan FJ (2014)	-2.751	0.171	0.029	-3.087	-2.416	-16.082	0.000		9.42	-0.86
Overall	-1.713	0.391	0.153	-2.479	-0.946	-4.379	0.000			

Heterogeneity test (I^2 = 98.208%, P < 0.001)
Z test (Z = -4.379, P < 0.001)
Random effects analysis

B

Creatinine
(Preoperative VS. Postoperative)

Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Std diff in means and 95%CI	Relative weight	Std Residual
Bachorzewska-Gajewska H (2007)	0.078	0.141	0.020	-0.199	0.355	0.550	0.582		9.96	1.05
Kato K (2008)	-0.372	0.153	0.023	-0.672	-0.072	-2.433	0.015		9.86	0.23
Rehman T (2008)	-0.014	0.141	0.020	-0.291	0.263	-0.098	0.922		9.96	0.89
Ishibashi Y (2010)	-0.110	0.334	0.111	-0.763	0.544	-0.328	0.743		7.82	0.62
Chen HQ (2011)	-0.103	0.154	0.024	-0.405	0.200	-0.664	0.507		9.85	0.72
Ribichini F (2012)	-2.319	0.334	0.111	-2.973	-1.665	-6.946	0.000		7.81	-2.91
Tanaga K (2012)	-0.511	0.339	0.115	-1.175	0.152	-1.510	0.131		7.75	-0.02
Chen ZF (2012)	-1.886	0.170	0.029	-2.219	-1.553	-11.096	0.000		9.70	-2.50
Zhao YY (2012)	-0.450	0.066	0.004	-0.580	-0.321	-6.834	0.000		10.46	0.09
Alharazy SM (2014)	0.098	0.427	0.182	-0.738	0.934	0.230	0.818		6.70	0.88
Pan FJ (2014)	-0.054	0.123	0.015	-0.294	0.186	-0.441	0.660		10.11	0.82
Overall	-0.499	0.182	0.033	-0.856	-0.142	-2.741	0.006			

Heterogeneity test (I^2 = 92.998%, P < 0.001)
Z test (Z = -2.741, P = 0.006)
Random effects analysis

C

eGFR
(Preoperative VS. Postoperative)

Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Std diff in means and 95%CI	Relative weight	Std Residual
Bachorzewska-Gajewska H (2007)	0.030	0.141	0.020	-0.247	0.307	0.213	0.831		32.06	0.19
Ishibashi Y (2010)	-0.960	0.352	0.124	-1.650	-0.270	-2.728	0.006		20.07	-1.96
Chen HQ (2011)	0.391	0.156	0.024	0.086	0.696	2.510	0.012		31.29	1.22
Alharazy SM (2014)	0.150	0.427	0.182	-0.687	0.987	0.350	0.726		16.58	0.35
Overall	-0.036	0.236	0.056	-0.499	0.427	-0.152	0.879			

Heterogeneity test (I^2 = 76.594%, P = 0.005)
Z test (Z = -0.152, P = 0.879)
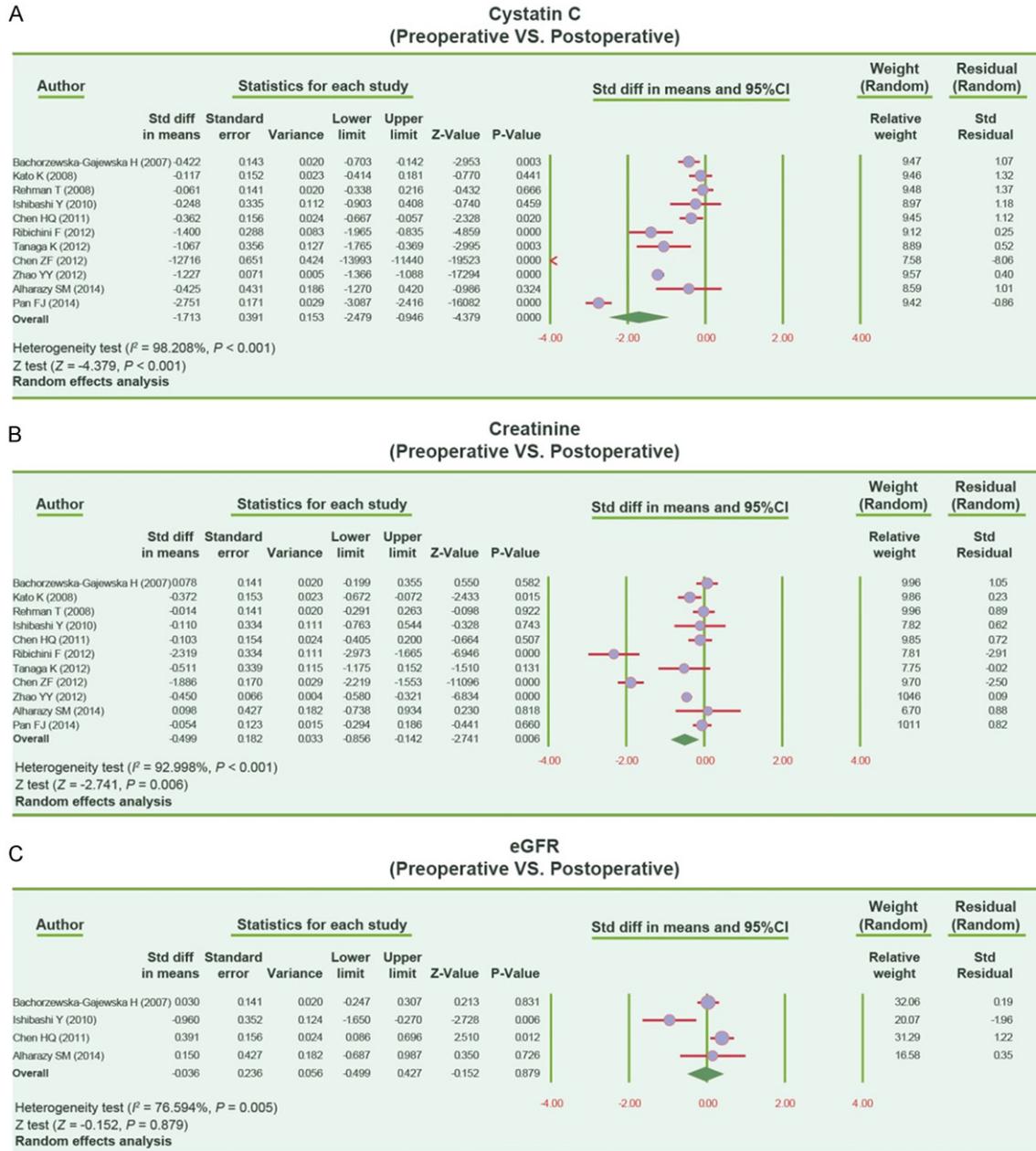Random effects analysis

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).

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 1153 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

A

Cystatin C
(Ethnicity: Preoperative VS. Postoperative)

Group by Ethnicity	Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Relative weight	Std Residual
Asians	Kato K (2008)	-0.117	0.152	0.023	-0.414	0.181	-0.770	0.441	12.97	1.48
Asians	Ishibashi Y (2010)	-0.248	0.335	0.112	-0.903	0.408	-0.740	0.459	12.49	1.35
Asians	Chen HQ (2011)	-0.362	0.156	0.024	-0.667	-0.057	-2.328	0.020	12.97	1.30
Asians	Tanaga K (2012)	-1.067	0.356	0.127	-1.765	-0.369	-2.995	0.003	12.41	0.78
Asians	Chen ZF (2012)	-12.716	0.424		-13.993	-11.440	-19.523	0.000	11.03	-6.81
Asians	Zhao YY (2012)	-1.227	0.071	0.005	-1.366	-1.088	-17.294	0.000	13.08	0.69
Asians	Alharazy SM (2014)	-0.425	0.431	0.186	-1.270	0.420	-0.986	0.324	12.11	1.21
Asians	Pan FJ (2014)	-2.751	0.171	0.029	-3.087	-2.416	-16.082	0.000	12.94	-0.39
Asians		-2.196	0.544	0.296	-3.262	-1.131	-4.039	0.000		
Caucasians	Bachorzewska-Gajewska H (2007)	-0.422	0.143	0.020	-0.703	-0.142	-2.953	0.003	35.62	0.37
Caucasians	Rehman T (2008)	-0.061	0.141	0.020	-0.338	0.216	-0.432	0.666	35.68	1.26
Caucasians	Ribichini F (2012)	-1.400	0.288	0.083	-1.965	-0.835	-4.859	0.000	28.70	-1.72
Caucasians		-0.574	0.304	0.093	-1.170	0.022	-1.887	0.059		

Asians: Z test (Z = -4.039, P < 0.001)
Caucasians: Z test (Z = -1.887, P = 0.059)

B

Creatinine
(Ethnicity: Preoperative VS. Postoperative)

Group by Ethnicity	Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Relative weight	Std Residual
Asians	Kato K (2008)	-0.372	0.153	0.023	-0.672	-0.072	-2.433	0.015	13.75	0.15
Asians	Ishibashi Y (2010)	-0.110	0.334	0.111	-0.763	0.544	-0.328	0.743	10.65	0.58
Asians	Chen HQ (2011)	-0.103	0.154	0.024	-0.405	0.200	-0.664	0.507	13.73	0.68
Asians	Tanaga K (2012)	-0.511	0.339	0.115	-1.175	0.152	-1.510	0.131	10.56	-0.10
Asians	Chen ZF (2012)	-1.886	0.170	0.029	-2.219	-1.553	-11.096	0.000	13.50	-2.78
Asians	Zhao YY (2012)	-0.450	0.066	0.004	-0.580	-0.321	-6.834	0.000	14.67	-0.00
Asians	Alharazy SM (2014)	0.098	0.427	0.182	-0.738	0.934	0.230	0.818	9.01	0.85
Asians	Pan FJ (2014)	-0.054	0.123	0.015	-0.294	0.186	-0.441	0.660	14.14	0.79
Asians		-0.450	0.204	0.042	-0.850	-0.051	-2.210	0.027		
Caucasians	Bachorzewska-Gajewska H (2007)	0.078	0.141	0.020	-0.199	0.355	0.550	0.582	34.63	1.12
Caucasians	Rehman T (2008)	-0.014	0.141	0.020	-0.291	0.263	-0.098	0.922	34.63	0.99
Caucasians	Ribichini F (2012)	-2.319	0.334	0.111	-2.973	-1.665	-6.946	0.000	30.73	-2.17
Caucasians		-0.691	0.500	0.250	-1.670	0.289	-1.382	0.167		

Asians: Z test (Z = -2.210, P = 0.027)
Caucasians: Z test (Z = -1.382, P = 0.167)

C

eGFR
(Ethnicity: Preoperative VS. Postoperative)

Group by Ethnicity	Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Relative weight	Std Residual
Asians	Ishibashi Y (2010)	-0.960	0.352	0.124	-1.650	-0.270	-2.728	0.006	32.13	-1.33
Asians	Chen HQ (2011)	0.391	0.156	0.024	0.086	0.696	2.510	0.012	38.62	0.92
Asians	Alharazy SM (2014)	0.150	0.427	0.182	-0.687	0.987	0.350	0.726	29.25	0.39
Asians		-0.114	0.436	0.190	-0.969	0.742	-0.261	0.794		
Caucasians	Bachorzewska-Gajewska H (2007)	0.030	0.141	0.020	-0.247	0.307	0.213	0.831	100.00	-0.02
Caucasians		0.030	0.141	0.020	-0.247	0.307	0.213	0.831		

Asians: Z test (Z = -0.261, P = 0.794)
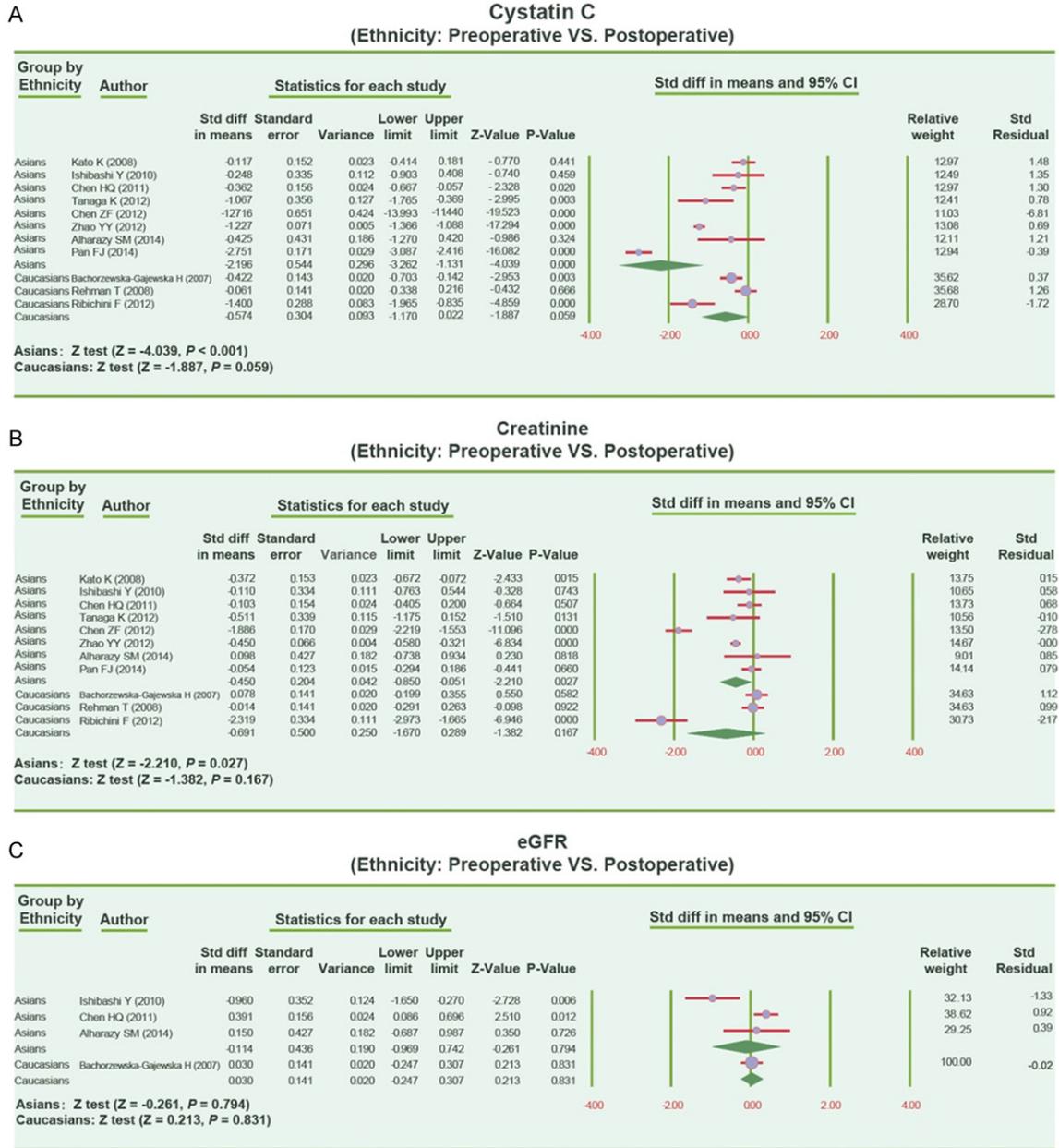Caucasians: Z test (Z = 0.213, P = 0.831)

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).

due to heterogeneity among studies (I^2 = 98.208%, P_h < 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 = -1.713, 95% CI = -2.479~-0.946, P < 0.001) (**Figure 2A**). A subgroup analysis based on ethnicity demonstrated that serum cystatin C level in CIN patients after PCI therapy was signif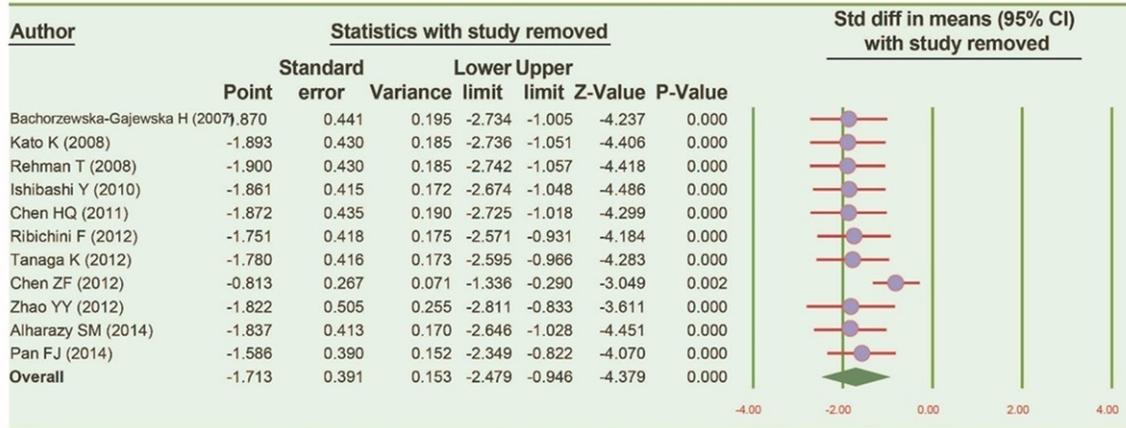icantly lower than before PCI therapy among Asians (SMD = -2.196, 95% CI = -3.262~-1.131, P < 0.001), but not among Caucasians (SMD = -0.574, 95% CI = -1.170~0.022, P = 0.059) (**Figure 3A**).

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

A

Cystatin C
(Preoperative vs. Postoperative)
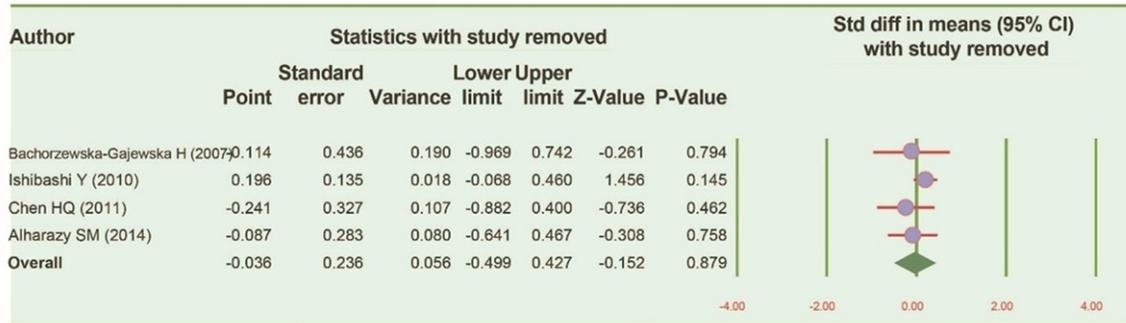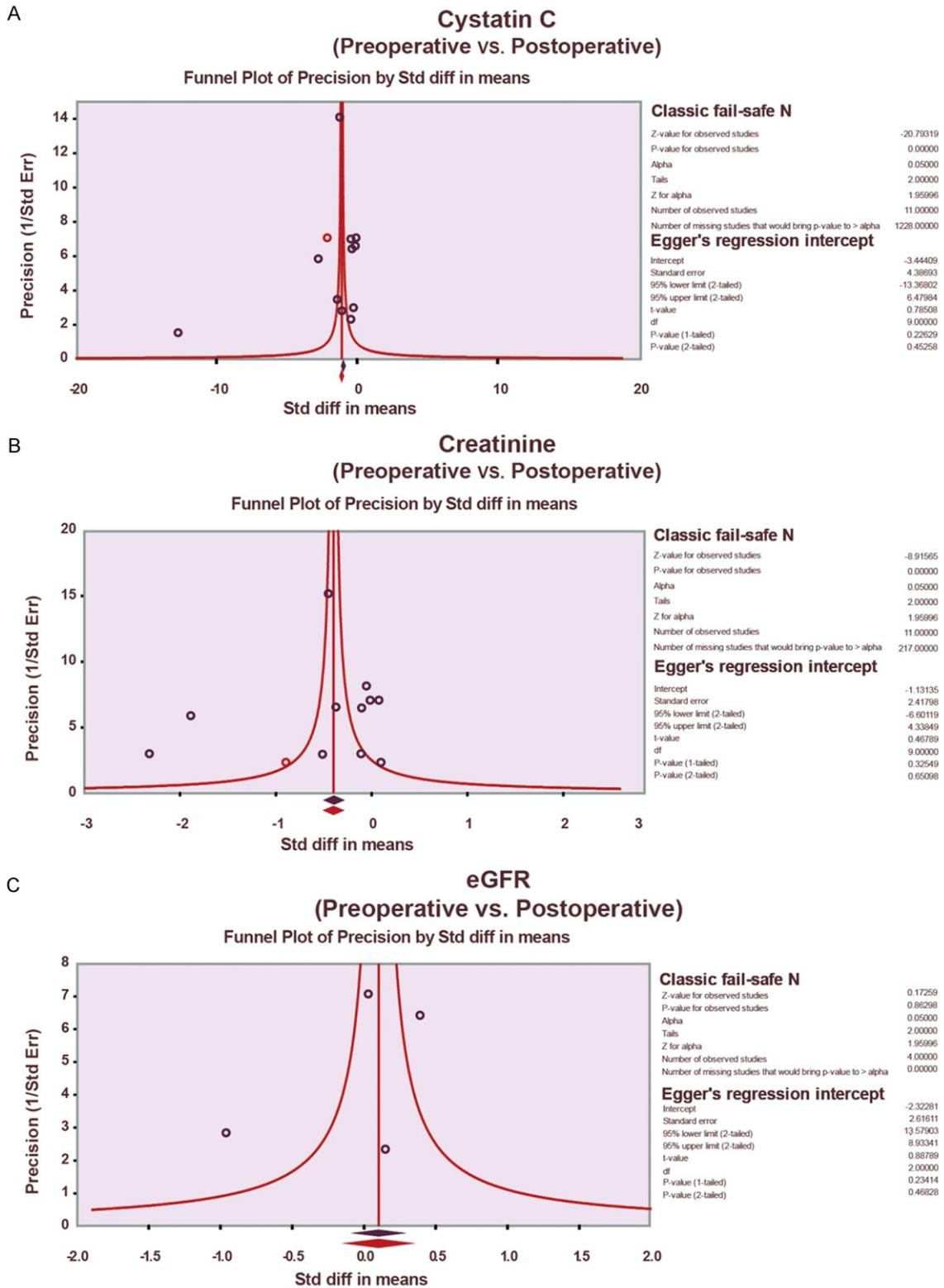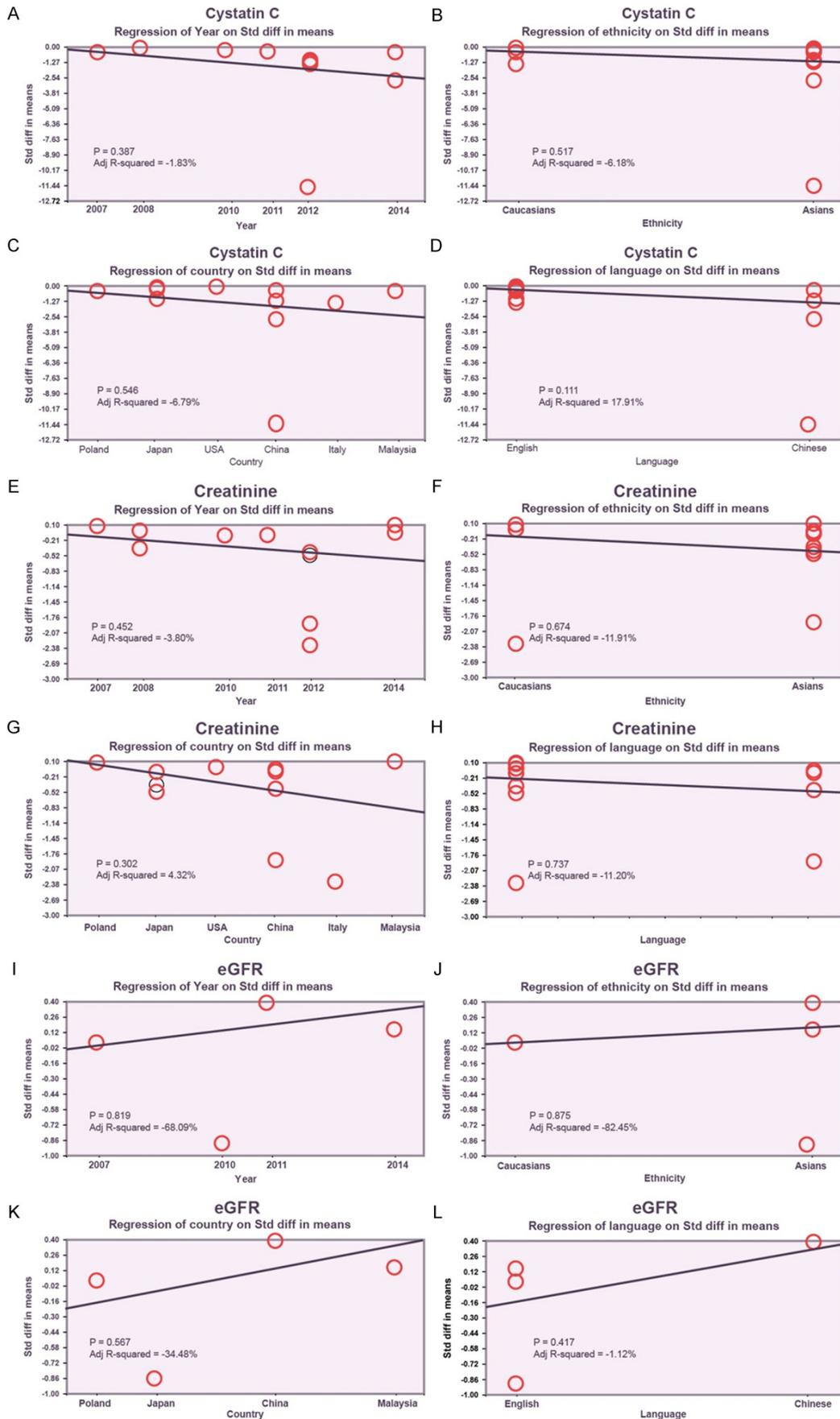
Author	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value
Bachorzewska-Gajewska H (2007)	-1.870	0.441	0.195	-2.734	-1.005	-4.237	0.000
Kato K (2008)	-1.893	0.430	0.185	-2.736	-1.051	-4.406	0.000
Rehman T (2008)	-1.900	0.430	0.185	-2.742	-1.057	-4.418	0.000
Ishibashi Y (2010)	-1.861	0.415	0.172	-2.674	-1.048	-4.486	0.000
Chen HQ (2011)	-1.872	0.435	0.190	-2.725	-1.018	-4.299	0.000
Ribichini F (2012)	-1.751	0.418	0.175	-2.571	-0.931	-4.184	0.000
Tanaga K (2012)	-1.780	0.416	0.173	-2.595	-0.966	-4.283	0.000
Chen ZF (2012)	-0.813	0.267	0.071	-1.336	-0.290	-3.049	0.002
Zhao YY (2012)	-1.822	0.505	0.255	-2.811	-0.833	-3.611	0.000
Alharazy SM (2014)	-1.837	0.413	0.170	-2.646	-1.028	-4.451	0.000
Pan FJ (2014)	-1.586	0.390	0.152	-2.349	-0.822	-4.070	0.000
Overall	-1.713	0.391	0.153	-2.479	-0.946	-4.379	0.000

Std diff in means (95% CI) with study removed: -4.00, -2.00, 0.00, 2.00, 4.00

B

Creatinine
(Preoperative vs. Postoperative)

Author	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value
Bachorzewska-Gajewska H (2007)	-0.563	0.197	0.039	-0.949	-0.178	-2.865	0.004
Kato K (2008)	-0.515	0.203	0.041	-0.913	-0.117	-2.535	0.011
Rehman T (2008)	-0.554	0.200	0.040	-0.945	-0.162	-2.773	0.006
Ishibashi Y (2010)	-0.532	0.192	0.037	-0.909	-0.156	-2.774	0.006
Chen HQ (2011)	-0.543	0.200	0.040	-0.936	-0.151	-2.714	0.007
Ribichini F (2012)	-0.347	0.169	0.029	-0.678	-0.015	-2.046	0.041
Tanaga K (2012)	-0.498	0.192	0.037	-0.875	-0.122	-2.593	0.010
Chen ZF (2012)	-0.325	0.135	0.018	-0.589	-0.061	-2.410	0.016
Zhao YY (2012)	-0.510	0.234	0.055	-0.968	-0.052	-2.182	0.029
Alharazy SM (2014)	-0.542	0.190	0.036	-0.914	-0.171	-2.860	0.004
Pan FJ (2014)	-0.550	0.203	0.041	-0.949	-0.152	-2.706	0.007
	-0.499	0.182	0.033	-0.856	-0.142	-2.741	0.006

Std diff in means (95% CI) with study removed: -4.00, -2.00, 0.00, 2.00, 4.00

C

eGFR
(Preoperative vs. Postoperative)

Author	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value
Bachorzewska-Gajewska H (2007)	-0.114	0.436	0.190	-0.969	0.742	-0.261	0.794
Ishibashi Y (2010)	0.196	0.135	0.018	-0.068	0.460	1.456	0.145
Chen HQ (2011)	-0.241	0.327	0.107	-0.882	0.400	-0.736	0.462
Alharazy SM (2014)	-0.087	0.283	0.080	-0.641	0.467	-0.308	0.758
Overall	-0.036	0.236	0.056	-0.499	0.427	-0.152	0.879

Std diff in means (95% CI) with study removed: -4.00, -2.00, 0.00, 2.00, 4.00

Figure 4. Sensitivity analyses of the influence of percutaneous coronary intervention in contrast-induced nephropathy patients' serum cystatin C, creatinine level and eGFR (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

A

B

C

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

Figure 6. Meta-regression analyses of the influence of percutaneous coronary intervention in contrast-induced nephropathy patients' serum cystatin C, creatinine level and eGFR.

Table 2. Meta-regression analysis of potential source of heterogeneity

	Heterogeneity factors	Coefficient	SE	t	P (Adjusted)	95% CI	
						LL	UL
Cystatin C	Year	-0.274	1.053	-0.26	1	-2.852	2.303
	Ethnicity	0.711	3.722	0.19	1	-8.397	9.818
	Country	0.211	1.468	0.14	1	-3.381	3.803
	Language	-3.614	2.991	-1.21	0.584	-10.932	3.703
Creatinine	Year	-0.098	0.246	-0.4	0.985	-0.699	0.503
	Ethnicity	0.657	0.872	0.75	0.864	-1.477	2.791
	Country	-0.079	0.349	-0.23	1	-0.932	0.774
	Language	-0.165	0.707	-0.23	1	-1.895	1.566
eGFR	Year	0.037	0.142	0.26	0.819	-0.574	0.648
	Ethnicity	-0.141	0.794	-0.18	0.914	-3.559	3.276
	Country	0.117	0.172	0.68	0.565	-0.622	0.856
	Language	0.632	0.623	1.02	0.415	-2.047	3.311

SE: Standard Error; LL: Lower Limit; UL: Upper Limit; eGFR: estimated glomerularfiltration rate.

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) ≥ 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 infraction, acute coronary syndrome and complex disease such as left main coronary disease and multi-vessel disease [48, 49]. PCI therapy includes a deflat-

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 inserum 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 abs-

ence 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.

Acknowledgements

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

References

[1] Solomon RJ, Mehran R, Natarajan MK, Doucet S, Katholi RE, Staniloae CS, Sharma SK, Labinaz M, Gelormini JL, Barrett BJ. Contrast-induced nephropathy and long-term adverse events: cause and effect? Clin J Am Soc Nephrol 2009; 4: 1162-1169.

[2] Ozhan H, Erden I, Ordu S, Aydin M, Caglar O, Basar C, Yalcin S, Alemdar R. Efficacy of short-term high-dose atorvastatin for prevention of contrast-induced nephropathy in patients undergoing coronary angiography. Angiology 2010; 61: 711-714.

[3] Ferrenberg AM and Swendsen RH. New Monte Carlo technique for studying phase transitions, Phys Rev Lett 1988; 61: 2635-2638.

[4] Maliborski A, Zukowski P, Nowicki G, Bogusławska R. Contrast-induced nephropathy--a review of current literature and guidelines. Med Sci Monit 2011; 17: RA199-204.

[5] Moos SI, van Vemde DN, Stoker J, Bipat S. Contrast induced nephropathy in patients undergoing intravenous (IV) contrast enhanced computed tomography (CECT) and the relationship with risk factors: a meta-analysis. Eur J Radiol 2013; 82: e387-399.

[6] Mohammed NM, Mahfouz A, Achkar K, Rafie IM, Hajar R. Contrast-induced Nephropathy. Heart Views 2013; 14: 106-116.

[7] Kunadian V, Zaman A, Spyridopoulos I, Qiu W. Sodium bicarbonate for the prevention of contrast induced nephropathy: a meta-analysis of published clinical trials. Eur J Radiol 2011; 79: 48-55.

[8] Reddan D, Laville M and Garovic VD. Contrast-induced nephropathy and its prevention: What do we really know from evidence-based findings? J Nephrol 2009; 22: 333-351.

[9] Stacul F, van der Molen AJ, Reimer P, Webb JA, Thomsen HS, Morcos SK, Almén T, Aspelin P, Bellin MF, Clement O, Heinz-Peer G; Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol 2011; 21: 2527-2541.

[10] Baerlocher MO, Asch M and Myers A. Contrast-induced nephropathy. CMAJ 2010; 182: 1445.

[11] Senoo T, Motohiro M, Kamihata H, Yamamoto S, Isono T, Manabe K, Sakuma T, Yoshida S, Sutani Y, Iwasaka T. Contrast-induced nephropathy in patients undergoing emergency percutaneous coronary intervention for acute coronary syndrome, Am J Cardiol 2010; 105: 624-628.

[12] Mautone A and Brown JR. Contrast-induced nephropathy in patients undergoing elective and urgent procedures. J Interv Cardiol 2010; 23: 78-85.

[13] Ad-hoc working group of ERBP, Fliser D, Laville M, Covic A, Fouque D, Vanholder R, Juillard L, Van Biesen W. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. Nephrol Dial Transplant 2012; 27: 4263-4272.

[14] Kwok CS, Pang CL, Yeong JK, Loke YK. Measures used to treat contrast-induced nephropathy: overview of reviews. Br J Radiol 2013; 86: 20120272.

[15] Nyklíček I, Dijksman SC, Lenders PJ, Fonteijn WA, Koolen JJ. A brief mindfulness based intervention for increase in emotional well-being and quality of life in percutaneous coronary intervention (PCI) patients: the MindfulHeart randomized controlled trial. J Behav Med 2014; 37: 135-144.

[16] Marenzi G, Assanelli E, Campodonico J, Lauri G, Marana I, De Metrio M, Moltrasio M, Grazi M, Rubino M, Veglia F, Fabbiocchi F, Bartorelli AL. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. Ann Intern Med 2009; 150: 170-177.

[17] Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013; 381: 629-638.

[18] Prasad A and Herrmann J. Myocardial infarction due to percutaneous coronary intervention. N Engl J Med 2011; 364: 453-464.

[19] F., L.P. Percutaneous coronary intervention. Medicine 2014; 42: 9.

[20] Vink MA, Dirksen MT, Suttorp MJ, Tijssen JG, van Etten J, Patterson MS, Slagboom T, Kiemeneij F, Laarman GJ. 5-year follow-up after primary percutaneous coronary intervention with a paclitaxel-eluting stent versus a bare-metal stent in acute ST-segment elevation myocardial infarction: a follow-up study of the PASSION (Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation) trial. JACC Cardiovasc Interv 2011; 4: 24-29.

[21] Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG; PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction, N Engl J Med 2013; 369: 1115-1123.

[22] Cockburn J, Hildick-Smith D, Cotton J, Doshi S, Hanratty C, Ludman P, Robinson D, Redwood S, de Belder M, de Belder A. Contemporary clinical outcomes of patients treated with or without rotational coronary atherectomy--an analysis of the UK central cardiac audit database. Int J Cardiol 2014; 170: 381-387.

[23] Alharazy SM, Kong N, Saidin R, Gafor AH, Maskon O, Mohd M, Zakaria SZ. Serum neutrophil gelatinase-associated lipocalin and cystatin C are early biomarkers of contrast-induced nephropathy after coronary angiography in patients with chronic kidney disease. Angiology 2014; 65: 436-442.

[24] Yang Z and Rannala B. Bayesian species delimitation using multilocus sequence data. Proc Natl Acad Sci U S A 2010; 107: 9264-9269.

[25] Shaker OG, El-Shehaby A and El-Khatib M. Early diagnostic markers for contrast nephropathy in patients undergoing coronary angiography. Angiology 2010; 61: 731-736.

[26] Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, Malyszko JS, Pawlak K, Mysliwiec M, Lawnicki S, Szmitkowski M, Dobrzycki S. Could neutrophil-gelatinase-associated lipocalin and cystatin C predict the development of

contrast-induced nephropathy after percutaneous coronary interventions in patients with stable angina and normal serum creatinine values? Kidney Blood Press Res 2007; 30: 408-415.

[27] Ishibashi Y, Yamauchi M, Musha H, Mikami T, Kawasaki K, Miyake F. Impact of contrast-induced nephropathy and cardiovascular events by serum cystatin C in renal insufficiency patients undergoing cardiac catheterization. Angiology 2010; 61: 724-730.

[28] Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003; 73: 712-716.

[29] Chen H, Manning AK and Dupuis J. A method of moments estimator for random effect multivariate meta-analysis. Biometrics 2012; 68: 1278-1284.

[30] Jackson D, White IR and Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med 2012; 31: 3805-3820.

[31] Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. JAMA 2006; 295: 676-680.

[32] Zintzaras E and Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. Genet Epidemiol 2005; 28: 123-137.

[33] Huizenga HM, Visser I and Dolan CV. Testing overall and moderator effects in random effects meta-regression. Br J Math Stat Psychol 2011; 64: 1-19.

[34] Sterne JA and Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis, J Clin Epidemiol 2001; 54: 1046-1055.

[35] Wikstrom EA, Naik S, Lodha N, Cauraugh JH. Balance capabilities after lateral ankle trauma and intervention: a meta-analysis. Med Sci Sports Exerc 2009; 41: 1287-1295.

[36] Kato K, Sato N, Yamamoto T, Iwasaki YK, Tanaka K, Mizuno K. Valuable markers for contrast-induced nephropathy in patients undergoing cardiac catheterization, Circ J 2008; 72: 1499-1505.

[37] Rehman T, Fought J and Solomon R. N-acetyl-cysteine effect on serum creatinine and cystatin C levels in CKD patients. Clin J Am Soc Nephrol 2008; 3: 1610-1614.

[38] Chen HQ, Min XW and Zhao LB. Evaluation of serum cystatin c on the superiority of contrast-induced nephropathy after percutaneous coronary intervention. China Journal of Modern Medicine 2011; 4165-4167.

[39] Chen ZF, Xu YL, Zhou JG and Niu WG. Effect of Cystatin c on contrast-induced nephropathy in

early diagnosis. Chinese Journal of Misdiagnostics 2012; 1832-1833.

[40] Ribichini F, Gambaro G, Graziani MS, Pighi M, Pesarini G, Pasoli P, Anselmi M, Ferrero V, Yabarek T, Sorio A, Rizzotti P, Lupo A, Vassanelli C. Comparison of serum creatinine and cystatin C for early diagnosis of contrast-induced nephropathy after coronary angiography and interventions. Clin Chem 2012; 58: 458-464.

[41] Tanaga K, Tarao K, Nakamura Y, Inoue T, Jo K, Ishikawa T, Miyazaki A. Percutaneous coronary intervention causes increase of serum cystatin C concentration even in the patients with a low risk of contrast-induced nephropathy. Cardiovasc Interv Ther 2012; 27: 168-173.

[42] Zhao YY, Ou YJ, Wang JS, Zhang WZ, Zhang WJ, Meng JQ, Shen PX, Liu D and Tang JM. Value of serum cystatin c in the early diagnosis of contrast-induced nephropathy. Journal of Zhengzhou University (Medical Sciences) 2012; 830-832.

[43] Pan FJ, Han ZH and Zhu QH. Serum cystatin c for early assessment of contrast-induced nephropathy. Modern Journal of Integrated Traditional Chinese and Western Medicine 2014; 1859-1860.

[44] Slocum NK, Grossman PM, Moscucci M, Smith DE, Aronow HD, Dixon SR, Share D, Gurm HS. The changing definition of contrast-induced nephropathy and its clinical implications: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). Am Heart J 2012; 163: 829-834.

[45] Bell RM, Rear R, Cunningham J, Dawnay A, Yellon DM. Effect of remote ischaemic conditioning on contrast-induced nephropathy in patients undergoing elective coronary angiography (ERICCIN): rationale and study design of a randomised single-centre, double-blind placebo-controlled trial. Clin Res Cardiol 2014; 103: 203-209.

[46] Wong PC, Li Z, Guo J and Zhang A. Pathophysiology of contrast-induced nephropathy. Int J Cardiol 2012; 158: 186-192.

[47] Santos RO, Malvar B, Silva R, Ramalho V, Pessegueiro P, Amoedo M, Aniceto J, Pires C. [Contrast-induced nephropathy]. Acta Med Port 2011; 24: 809-820.

[48] Testa L and Bedogni F. Treatment of saphenous vein graft disease: "never ending story" of the "eternal return". Res Cardiovasc Med 2014; 3: e21092.

[49] Borden WB, Redberg RF, Mushlin AI, Dai D, Kaltenbach LA, Spertus JA. Patterns and intensity of medical therapy in patients undergoing percutaneous coronary intervention. JAMA 2011; 305: 1882-1889.

[50] Li J, Zhang Y, Cui L, Wang J, Pang X, Lai Y, Yao Y, Liu X, Li Y. Mechanical stretch changes coro-

nary artery fibroblasts function by upregulating HSF1 protein expression. Int J Biol Macromol 2013; 59: 105-110.

[51] De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012; 367: 991-1001.

[52] Chan PS, Patel MR, Klein LW, Krone RJ, Dehmer GJ, Kennedy K, Nallamothu BK, Weaver WD, Masoudi FA, Rumsfeld JS, Brindis RG, Spertus JA. Appropriateness of percutaneous coronary intervention. JAMA 2011; 306: 53-61.

[53] Patti G, Ricottini E, Nusca A, Colonna G, Pasceri V, D'Ambrosio A, Montinaro A, Di Sciascio G. Short-term, high-dose Atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN [atorvastatin for reduction of myocardial damage during angioplasty--contrast-induced nephropathy] trial. Am J Cardiol 2011; 108: 1-7.