

# Impact of low hemoglobin on the development of contrast-induced nephropathy: A retrospective cohort study

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Received May 7, 2015; Accepted March 31, 2016

DOI: 10.3892/etm.2016.3416

**Abstract.** An increase in the use of iodinated contrast media, such as iohexol, iodixanol, iopamidol and iopromide, occasionally causes contrast-induced nephropathy (CIN) in patients undergoing coronary angiography (CAG) and/or percutaneous coronary intervention (PCI). The present study aimed to assess the effects of low levels of hemoglobin on the development of CIN in patients with normal renal function following CAG/PCI. A total of 841 consecutive patients undergoing CAG/PCI were divided into two groups: Patients with low levels of hemoglobin (male, <120 g/l; female, <110 g/l; n=156) and normal levels of hemoglobin (male, 120-160 g/l; female, 110-150 g/l; n=685). Multiple logistic regression analysis was performed to identify risk factors for CIN, which developed in 14.7% of patients with low levels of hemoglobin (relative

risk, 3.07) and 5% of patients with normal levels of hemoglobin (P<0.01). Independent risk factors for developing CIN in patients with low levels of hemoglobin were a contrast media volume  $\geq 200$  ml, diuretic usage, low levels of hemoglobin and diabetes mellitus. For the patients with normal hemoglobin levels, the independent risk factors for developing CIN were a contrast media volume  $\geq 200$  ml and diuretic usage. The change in serum creatinine in patients with low levels of hemoglobin was significantly greater compared with patients with normal levels of hemoglobin (7.35 $\pm$ 22.60 vs. 1.40 $\pm$ 12.00; P<0.01). A similar incidence of developing CIN was observed when patients were administered each type of contrast media: Iohexol, iodixanol, iopamidol and iopromide. The optimal cut-off point at which the serum hemoglobin concentration resulted in a high probability of developing CIN was determined as 111.5 g/l in females and 115.5 g/l in males. In conclusion, low levels of hemoglobin were observed to be an independent risk factor for developing CIN. Patients with reduced hemoglobin levels should, therefore, be closely monitored prior to, and during, the administration of iodinated contrast media.

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*Abbreviations:* CAG, coronary angiography; CIN, contrast-induced nephropathy; PCI, percutaneous coronary intervention

*Key words:* low hemoglobin, contrast media, contrast-induced nephropathy

## Introduction

Iodinated contrast media used in diagnostic and therapeutic procedures often causes nephrotoxicity (1). Contrast-induced nephropathy (CIN) is one of the main adverse effects of iodinated contrast media in patients undergoing coronary angiography (CAG) and/or percutaneous coronary intervention (PCI) (2). CIN refers to an impairment of renal function (usually defined as the elevation of serum creatinine levels by 0.5 mg/dl or 25%) that occurs within 3 days following intravascular administration of contrast media, with the exclusion of other causes (3,4). CIN is independently associated with a longer stay in hospital, and results in increased long-term

mortality and increased costs of medical care that partly result from the prolonged hospital stay (5,6).

The incidence of CIN can be as high as 50% for high risk patients (3,4,7). Risk factors associated with CIN include the type and dosage of contrast media, concomitant nephrotoxic medication, inflammation, diabetes mellitus, renal insufficiency, congestive heart failure, increasing age and female gender (5-10). The presence of multiple risk factors concomitantly can increase the risk of CIN disproportionately (7). A key step in minimizing the risk of developing CIN is to identify patients at risk and initiate appropriate prophylactic measures (6).

When multiple risk factors coexist, patients with low baseline hematocrit are reported to have a higher incidence of CIN (11), suggesting that anemia may be a risk factor for CIN. Low levels of hemoglobin may cause hypoxia owing to the decreased oxygen transport capacity (12) and their increased affinity for oxygen when exposed to contrast media (13), which aggravates hypoxic injury and further results in renal dysfunction (14,15). However, few studies have assessed the effects of low hemoglobin levels on CIN in patients without baseline renal insufficiency. In the present study, an investigation into whether low levels of hemoglobin are associated with an increased incidence of CIN in patients undergoing CAG and/or PCI was performed.

## Materials and methods

*Study population and exclusion criteria.* The present retrospective study included 841 patients (565 males and 276 females; aged  $64.92 \pm 10.80$  years) who had been diagnosed with coronary heart disease and had undergone CAG/PCI at the Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China), the Affiliated Wenling Hospital of Wenzhou Medical University (Wenling, China) or Tongde Hospital of Zhejiang Province (Hangzhou, China) between January 2013 and December 2013. Patients with baseline renal insufficiency, tumor-associated anemia, severe infection, cardiogenic shock and any diseases resulting in abnormal levels of hemoglobin (such as chronic pulmonary heart disease and congestive heart failure) were excluded from the present study. Patients who had been exposed to nephrotoxic medication (aminoglycosides and non-steroidal anti-inflammatory drugs, with the exception of aspirin), N-acetylcysteine and interventional anemia management, with the exception of patients who had a diet of enriched foods prior to developing CIN, were also excluded. For patients who underwent multiple CAG/PCI procedures during the study period, only the first procedure was included for analysis.

In the study population, patients with comorbid coronary heart diseases, hypertension and diabetes mellitus, medication or treatment was provided according to corresponding guidelines, including the following: i) The European Society of Cardiology Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation or without persistent ST-segment elevation; ii) the guidelines of Chinese Hypertension League for the management of hypertension; and iii) Chinese Diabetes Society Guidelines for the management of diabetes (16-19). The demographic, clinical and laboratory data, including details of CAG/PCI, were

collected from study patients. Written informed consent was obtained from all patients.

*Clinical definitions.* Patients were divided into the following two groups according to their hemoglobin levels: i) Patients with low hemoglobin levels (hemoglobin-L group;  $n=156$ ); ii) and patients with normal hemoglobin levels (hemoglobin-N group;  $n=685$ ). Baseline renal insufficiency was defined as an increase in serum creatinine concentration  $>133 \mu\text{mol/l}$  (20). CIN was defined as an acute deterioration in renal function with an increase in serum creatinine of  $0.5 \text{ mg/dl}$  ( $50 \mu\text{mol/l}$ ), or 25% from the baseline within 96 h following the intravascular administration of contrast agents, in the absence of alternative risk factors. Anemia was defined as a hemoglobin concentration  $<120 \text{ g/l}$  for males and  $<110 \text{ g/l}$  for females, in accordance with the Chinese criteria (21).

*Treatment and measurements.* The patients were exposed to four contrast media, as follows: Iohexol [100 ml (30 g/l) or 50 ml (15 g/l); Shanghai General Pharmaceutical, Co., Ltd., Shanghai, China]; iodixanol [100 ml (32 g/l) or 50 ml (16 g/l); Shanghai General Pharmaceutical, Co., Ltd.]; iopamidol [100 ml (37 g/l) or 50 ml (18.5 g/l); Sine Pharmaceutical, Co., Ltd., Shanghai, China]; and iopromide [100 ml (30 g/l) or 50 ml (15 g/l); Bayer Vital GmbH, Leverkusen, Germany]. The patients received saline hydration within 3-12 h prior to and 6-24 h following CAG/PCI procedures, as described previously (22). Patient demographic, clinical and laboratory data, including details of the CAG/PCI, were collected. For patients with diabetes mellitus, the administration of metformin was withheld at least 24 h prior to the procedure, and replaced with insulin (NovoRapid 30, Novolin 30R or Novolin 70/30; Novo Nordisk A/S, Bagsvaerd, Denmark) or oral anti-diabetic drugs, including repaglinide tablets (Hansoh Pharmaceutical Co., Ltd., Jiangsu, China), Nateglinide tablets (Beijing Novartis Pharma Ltd., Beijing, China) or Acarbose tablets (Bayer HealthCare Company Ltd., Beijing, China). Blood samples (5 ml) were measured for serum creatinine, glucose, uric acid and lipids using an automatic biochemical analyzer (Roche Module P800; Roche Diagnostics, Basel, Switzerland) and hemoglobin was detected using a hematology analyzer (XE-2100; Sysmex Corporation, Kobe, Japan).

The baseline characteristics of patients in the hemoglobin-L and hemoglobin-N groups were compared. The incidence of CIN and changes in serum creatinine prior to and following CAG/PCI were analyzed. Serum creatinine measurements taken prior to CAG/PCI were recorded as the baseline creatinine level, and the post-procedure serum creatinine was recorded as the maximum creatinine level that was measured within 96 hours of CAG/PCI.

*Statistical analysis.* Statistical analysis was performed using SPSS version 20.0 (IBM SPSS, Armonk, NY, USA). Continuous data were expressed as the mean  $\pm$  standard deviation when normally distributed. Categorical data were expressed as the absolute value and percentage. Comparisons of continuous variables among the four contrast media were performed using one-way analysis of variance with multiple Scheffe-type comparisons after reciprocal transformation of the variables to correct for heterogeneity of variance. In order

Table I. Baseline characteristics of patients with normal (Hemoglobin-N) or low (Hemoglobin-L) levels of hemoglobin.

Parameter	Hemoglobin-N group (n=685)	Hemoglobin-L group (n=156)	P-value
Female, n (%)	218 (31.8%)	58 (37.2%)	0.20
Age (years)	63.56±10.72	70.79±9.00	<0.01
Body weight (kg)	63.17±11.44	61.95±12.05	0.24
Hypertension, n (%)	421 (61.5%)	100 (64.1%)	0.54
Diabetes mellitus, n (%)	135 (19.7%)	39 (25.0%)	0.14
Current smoking, n (%)	172 (25.1%)	30 (19.2%)	0.12
Medication used			
Aspirin, n (%)	672 (98.1%)	153 (98.1%)	1.00
Clopidogrel, n (%)	667 (97.4%)	150 (96.2%)	0.42
ACEI/ARB, n (%)	519 (75.8%)	127 (81.4%)	0.13
β-blocker, n (%)	468 (68.3%)	109 (69.9%)	0.70
Statin, n (%)	653 (95.3%)	151 (96.8%)	0.42
Anticoagulants, n (%)	300 (43.8%)	75 (48.1%)	0.33
CCB, n (%)	192 (28.0%)	23 (14.7%)	<0.01
PPI, n (%)	339 (49.5%)	102 (65.4%)	<0.01
Nitrate, n (%)	305 (44.5%)	74 (46.8%)	0.60
Diuretics, n (%)	139 (20.3%)	42 (26.9%)	0.069
LVEF (%)	60.98±9.63	61.40±11.17	0.67
Total cholesterol (mmol/l)	4.41±1.14	4.15±1.11	<0.01
Triglyceride (mmol/l)	1.75±1.22	1.30±0.74	<0.01
LDL-C (mmol/l)	2.64±0.97	2.51±0.95	0.13
Fasting blood glucose (mmol/l)	5.88±1.96	5.85±1.87	0.90
Uric acid (μmol/l)	355.85±98.12	356.20±120.69	0.97
Red blood cell (10 <sup>12</sup> /l)	4.39±0.43	3.61±0.44	<0.01
Hemoglobin (g/l)	134.04±12.70	105.11±11.39	<0.01
Hematocrit (%)	0.40±0.039	0.33±0.057	<0.01

Data are expressed as the mean + standard deviation or number (%) of patients. ACEI, acetylcholinesterase inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; PPI, proton pump inhibitor; LVEF, left ventricular ejection fraction; LDL-C, low density lipoprotein cholesterol.

to evaluate inter- and intra-group differences, continuous variables were compared using the paired t-test and independent-samples t-test, and categorical variables were compared using a  $\chi^2$  test or Fisher's exact test where appropriate. The Bonferroni correction was used for multiple comparisons. Univariate logistic regression was performed to search for the potential factor of CIN as a dependent variable. Variables that were statistically significant on univariate analysis and other potential variables were identified as predictors of CIN in the final multivariate model using the forward selection method. A two-sided 95% confidence interval (CI) was constructed around the point estimate of the relative risk. Receiver operating characteristic (ROC) curve analysis was performed to predict CIN. All tests were two-sided, and  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Patient characteristics.** As presented in Table I, patients in the hemoglobin-L group were significantly older compared with patients in the hemoglobin-N group (70.79±9.00 vs. 63.

56±10.72 years;  $P < 0.01$ ). The plasma levels of total cholesterol, triglycerides, red blood cells, hemoglobin and hematocrit in the hemoglobin-L group were significantly lower compared with those in the hemoglobin-N group ( $P < 0.05$ ). In the hemoglobin-L group, a greater number of patients used calcium channel blockers and a lower number of patients used proton pump inhibitors compared with the hemoglobin-N group ( $P < 0.05$ ). There was no significant difference between the groups regarding the incidence of CIN resulting from the contrast media used ( $P = 0.39$ ; Table II). Patients in both groups had been administered similar volumes of iohexol, iodixanol or iopamidol ( $P > 0.05$ ), but only a small volume of iopromide ( $P < 0.01$ ).

**Changes in levels of serum creatinine, incidence of CIN and hospital stay.** The mean serum creatinine concentration levels increased significantly following the intravascular administration of contrast media in both patient groups ( $P < 0.05$ ; Table III). However, the change in serum creatinine concentration levels prior to and following the use of contrast media in the hemoglobin-L group was significantly higher compared with the hemoglobin-N group ( $P < 0.01$ ).

Table II. Contrast media volume used in patients undergoing CAG and/or PCI.

Parameter	Iohexol (n=177)	Iodixanol (n=133)	Iopamidol (n=260)	Iopromide (n=271)	P-value
Mean volume (ml)	137.49±86.40	127.33±63.02	125.63±64.30	98.49±51.17 <sup>a</sup>	<0.01
CIN, n (%)	10 (5.6%)	13 (9.8%)	19 (7.3%)	15 (5.5%)	0.39

<sup>a</sup>P<0.01, iopromide vs. iohexol, iodixanol or iopamidol; P=0.97, iohexol vs. iodixanol; P=0.99, iodixanol vs. iopamidol; P=0.85, iohexol vs. iopamidol. CAG, coronary angiography; PCI, percutaneous intervention; CIN, contrast-induced nephropathy.

Table III. Changes in serum creatinine and incidence of contrast-induced nephropathy in patients with normal (Hemoglobin-N) and low (Hemoglobin-L) levels of hemoglobin.

Parameter	Hemoglobin-N (n=685)	Hemoglobin-L (n=156)	P-value
Serum creatinine before use of contrast media ( $\mu\text{mol/l}$ )	78.00±18.41	80.31±23.35	0.31
Serum creatinine after use of contrast media ( $\mu\text{mol/l}$ )	79.40±18.67	87.65±33.49	<0.01
Absolute change in serum creatinine ( $\mu\text{mol/l}$ )	1.40±12.00	7.35±22.60	<0.01
CIN	34 (5.0)	23 (14.7)	<0.01
Females with CIN	9 (26.5)	10 (43.5)	0.18
Males with CIN	25 (73.5)	13 (56.5)	
Total duration of hospital stay (days)	7.52±4.03	8.87±4.87	<0.01
Duration of hospital stay after use of contrast media (days)	4.59±3.55	5.04±3.54	0.15

Data are expressed as the mean  $\pm$  standard deviation or n (%). CIN, contrast-induced nephropathy.

CIN occurred in 6.78% (57 of 841 patients) of the total patients in the study. Notably, there was no significant difference in the occurrence of CIN in genders between the two groups (females, 26.5 vs. 43.5%; males, 73.5 vs. 56.5%; P=0.18; Table III). Among the 57 patients who developed CIN, 12 (12/319, 3.76%) had received <100 ml contrast media, 23 (23/383, 6.00%) received 100-200 ml contrast media, and 22 (22/139, 15.83%) received  $\geq$ 200 ml contrast media (Fig. 1).

The mean total duration of hospital stay of patients in the hemoglobin-L group was 8.87±4.87 days, which was significantly longer than that of patients in the hemoglobin-N group (7.52±4.03 days; P<0.01). The mean duration of hospital stay following administration of the contrast media was not significantly different between the two groups (4.59±3.55 vs. 5.04±3.54 days; P=0.15).

**Risk factors associated with CIN.** In a univariate model, contrast media volume  $\geq$ 200 ml, diuretic use, low levels of hemoglobin, diabetes mellitus, hyperuricemia, use of anticoagulants and age  $\geq$ 70 years were associated with the development of CIN (P<0.05). Multivariate analysis was performed to evaluate these baseline univariate predictors. Contrast media volume  $\geq$ 200 ml (RR, 4.64; 95% CI, 2.15-9.99; P<0.01), diuretic usage (RR, 3.68; 95% CI, 2.07-6.53; P<0.01), low hemoglobin levels (RR, 3.07; 95% CI, 1.69-5.56; P<0.01) and diabetes mellitus (RR, 2.46; 95% CI, 1.35-4.46; P<0.01) were found to be associated with an increased risk of CIN in the hemoglobin-L group (Table IV). For the patients with normal hemoglobin levels, contrast media volume  $\geq$ 200 ml (RR, 4.56; 95% CI, 1.73-12.03; P<0.01) and diuretic usage (RR,

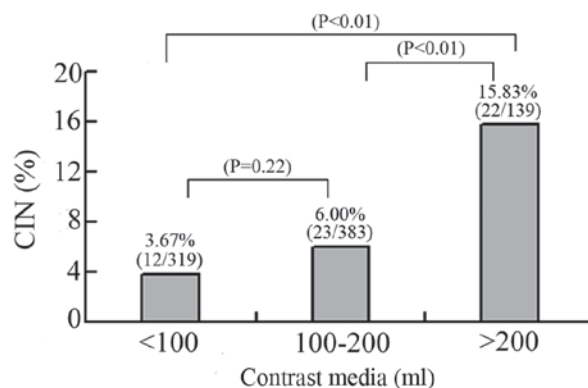


Figure 1. Incidence of CIN in patients who received different volumes of contrast media. A  $\chi^2$  test was performed to detect inter-group comparison. CIN, contrast-induced nephropathy.

3.31; 95% CI, 1.62-6.76; P<0.01) were shown to be associated with an increased risk of CIN (Table V).

**ROC.** ROC curve analysis was conducted to determine the cut-off point at which there is a high probability of developing CIN. Male and female patients were analyzed separately. It was observed that the optimal cut-off point of serum hemoglobin concentration for predicting CIN was 111.5 g/l in females, with a sensitivity of 63.2% and specificity of 76.3%, and an area under the curve (AUC) of 0.737 (P<0.01; Fig. 2). A serum hemoglobin concentration of 115.5 g/l was determined as the optimal cut-off point for predicting CIN in males, with a sensitivity of 34.2% and specificity of 89.2%, and an AUC of 0.625

Table IV. Risk factors associated with contrast-induced nephropathy in the hemoglobin-L group were determined by univariate and multivariate logistic regression analyses.

Variable	Univariate analysis			Multivariate analysis		
	RR	95% CI	P-value	RR	95% CI	P-value
Contrast media volume $\geq$ 200 ml	4.81	2.31-10.03	<0.01	4.64	2.15-9.99	<0.01
Use of diuretics	3.92	2.27-6.78	<0.01	3.68	2.07-6.53	<0.01
Low levels of hemoglobin	3.31	1.89-5.80	<0.01	3.07	1.69-5.56	<0.01
Diabetes mellitus	2.61	1.49-4.58	<0.01	2.46	1.35-4.46	<0.01
Hypercholesterolemia	2.14	1.23-3.70	<0.01			
Use of anticoagulants	2.44	1.39-4.28	<0.05			
Age $\geq$ 70 years	1.83	1.07-3.14	<0.05			
Use of PPI	1.60	0.92-2.80	0.096			
Contrast media volume 100-200 ml	1.63	0.80-3.34	0.18			
LDL-C	1.32	0.70-2.52	0.39			
Use of nitrates	1.20	0.70-2.05	0.51			
Use of statins	1.29	0.30-5.48	0.74			
Gender (female)	1.025	0.58-1.81	0.93			
Use of ACEI	1.02	0.54-1.94	0.94			

RR, relative risk; CI, confidence interval; PPI, proton pump inhibitor; LDL-C, low-density lipoprotein cholesterol; ACEI, acetylcholinesterase inhibitor.

Table V. Risk factors associated with contrast-induced nephropathy in the hemoglobin-N group were determined by univariate and multivariate logistic regression analyses.

Variable	Univariate analysis			Multivariate analysis		
	RR	95% CI	P-value	RR	95% CI	P-value
Contrast media volume $\geq$ 200 ml	4.53	1.73-11.82	<0.01	4.56	1.73-12.03	<0.01
Use of diuretics	3.29	1.63-6.65	<0.01	3.31	1.62-6.76	<0.01
Diabetes mellitus	2.34	1.13-4.86	0.02			
Use of anticoagulants	1.30	0.65-2.59	0.46			
Age	1.30	0.63-2.69	0.47			
Use of PPI	1.69	0.83-3.44	0.15			
Contrast media volume 100-200 ml	1.97	0.79-4.91	0.15			
LDL-C	1.33	0.59-3.02	0.49			
Use of nitrates	1.43	0.72-2.85	0.31			
Use of ACEI	1.25	0.53-2.92	0.61			
Smoking	1.08	0.49-2.36	0.85			
Total cholesterol	1.05	0.46-2.36	0.91			

RR, relative risk; CI, confidence interval; PPI, proton pump inhibitor; LDL-C, low-density lipoprotein cholesterol; ACEI, acetylcholinesterase inhibitor.

( $P < 0.01$ ; Fig. 3). Maintaining a concentration of hemoglobin  $>130$  g/l decreased the incidence of CIN by 26.3% and 25.8% for males and females respectively.

## Discussion

The present study demonstrated that patients with low levels of hemoglobin have a nearly three-fold higher incidence of

developing CIN compared with patients with normal levels of hemoglobin, suggesting that low hemoglobin is a strong risk factor for developing CIN. Furthermore, patients with low hemoglobin levels had longer total hospital stay. The cut-off hemoglobin values for predicting CIN were 115.5 g/l for male and 111.5 g/l for female patients.

In the current study, although the patients with low levels of hemoglobin were older, multivariate analysis did not identify

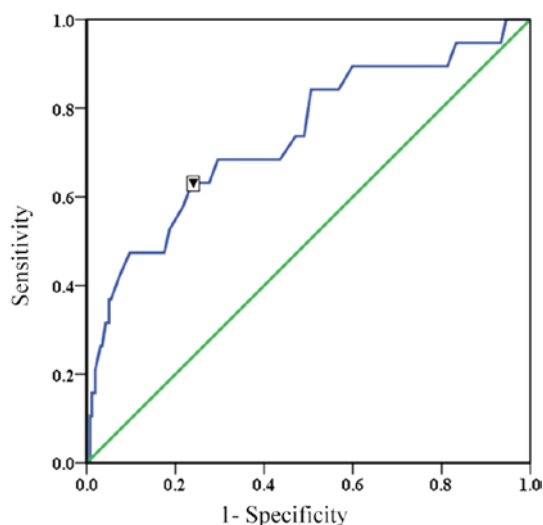


Figure 2. Receiver operating characteristic (ROC) curve analysis of serum hemoglobin concentration for predicting contrast-induced nephropathy in female patients. The triangle marks the cut-off point (111.5 g/l) for developing CIN; sensitivity, 63.2%; specificity, 76.3%; area under the ROC curve, 0.737; 95% CI, 0.607-0.866;  $P < 0.01$ .

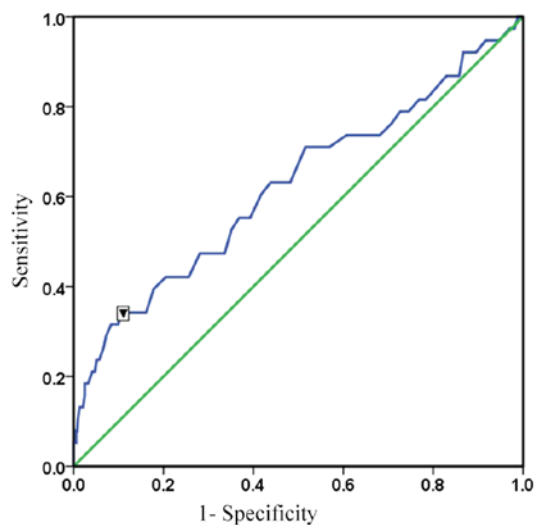


Figure 3. Receiver operating characteristic (ROC) curve analysis of serum hemoglobin concentration for predicting contrast-induced nephropathy in male patients. The triangle marks the cut-off point (115.5 g/l) for developing CIN; sensitivity, 34.2%; specificity, 89.2%; area under the ROC curve, 0.625; 95% CI, 0.520-0.729;  $P = 0.01$ .

age  $\geq 70$  years as a risk factor. It has been reported that patients  $\geq 70$  years have an increased risk of CIN (23,24); however, the reasoning behind this is multifactorial and partially due to the reduced renal function typically observed in elderly patients (7). Thus, it is reasonable to account for advanced age when planning the administration of contrast media.

Four different contrast media were investigated in the present study, including the iso-osmolality medium iodixanol and the low-osmolality media iohexol, iopamidol and iopromide. Iso-osmolality media are believed to cause a low incidence of CIN in comparison with low-osmolality media; however, this remains controversial (23). Solomon (25) reported that the risk of CIN was significantly lower with iodixanol and iopamidol compared with iohexol, but no significant difference was observed between iodixanol and iopamidol. In an earlier meta-analysis, it was observed that there was no difference in the incidence of CIN in patients without pre-existing renal insufficiency, or injury based on the use of contrast media with different osmolalities (26), and these results were consistent with the findings of the present study.

Besides renal injury and changes in serum creatinine, other risk factors of CIN have been reported, including high-dose contrast media, diuretic usage and diabetes (26-29). A previous study reported that the incidence of CIN increases with higher doses of contrast media (27), and in the present study, patients receiving  $\geq 200$  ml contrast media were more likely to suffer from CIN. However, patients had a similar risk of developing CIN when receiving  $< 100$  or 100-200 ml contrast media, suggesting that a potential safe range of contrast media is  $< 200$  ml. Thus, it is possible to decrease the incidence of CIN in patients undergoing CAG/PCI by reducing the dose of contrast media to  $< 200$  ml.

The association of diuretics with the development of CIN may be a result of their nephrotoxic potential, particularly in patients with pre-existing renal diseases (28). Patients treated with diuretics have been reported to have a greater incidence

of CIN (30), and it is recommended that diuretics should be discontinued for at least 24 h prior to the administration of contrast media, particularly when the glomerular filtration rate is  $< 60$  ml/min per  $1.73$  m<sup>2</sup> (28). The present study determined that the use of diuretics resulted in a high risk of developing of CIN (RR, 3.68; 95% CI, 2.07-6.53;  $P < 0.01$ ). However, diuretics have previously been reported to have a potentially protective effect against kidney injury (31,32). Due to these conflicts of evidence, a meta-analysis was performed to examine the clinical efficacy of furosemide administration in preventing CIN (33). Unexpectedly, furosemide, as a diuretic, has no additional influence beyond saline hydration on the incidence of CIN (33). However, the impact of furosemide dose on clinical outcome was not taken into account. In the present study, the mean daily dose of furosemide in patients with CIN was  $30.37 \pm 10.18$  mg, which is a higher dose than that used in similar studies (31). Thus, it remains to be demonstrated whether a high dose of diuretics is related to a higher risk of developing CIN.

Diabetic nephropathy has been identified as a strong and independent risk factor for CIN (34), which is consistent with the findings of the present study. In addition, individuals with diabetes, even in the absence of nephropathy, are more likely to develop CIN compared with non-diabetic individuals (4). Therefore, diabetes mellitus as a risk factor for developing CIN should not be underestimated, and patients with diabetes mellitus, regardless of whether they have renal dysfunction, should be evaluated closely prior to the administration of contrast media.

The impact that low hemoglobin levels have on the development of CIN has not been clearly identified. Previous studies have concluded that low levels of hemoglobin are not a risk factor for CIN (8,35,36), while one study observed that a reduction in hematocrit increased the incidence of CIN in patients with or without chronic kidney disease (RR, 1.23; 95% CI, 1.14-1.31;  $P < 0.01$ ) (11). It is likely that a number of these studies did not rigorously exclude the confounders

related to low hemoglobin or serum creatinine, such as chronic kidney disease. Low levels of hemoglobin may occur as a result of various conditions, such as immunological disease, malignancy, chemical exposure or chronic kidney disease, which results in difficulty in assessing the independent effects of hemoglobin on CIN (29,37-40). In the present study, however, low levels of hemoglobin were demonstrated to be an independent risk factor for CIN, increasing the risk by 3.07 (95% CI, 1.69-5.56;  $P < 0.01$ ), although it was not the highest risk factor for CIN and was second to contrast media volume  $\geq 200$  ml and the use of diuretics. An ROC analysis for male and female patients separately was performed in the present study, and it was determined that the different cut-off values of serum hemoglobin for developing CIN in males and females was different, emphasizing that gender should be taken into account when assessing the risk of developing CIN.

It is important to note that low hemoglobin levels are often associated with poor prognosis and mortality in patients (41). It has been reported that there is a dose-dependent increase in mortality when hemoglobin levels decrease below the optimal hemoglobin range (42). The risk of mortality increases 2.5 times for every gram reduction in hemoglobin  $< 80$  mg/l (43). Furthermore, Shah *et al* (42) reported that the risk associated with low levels of hemoglobin is greater in patients with myocardial infarction than for those with stable angina. Therefore, a previous study treated anemic patients with myocardial injury with blood transfusions and demonstrated favorable outcomes (44). In addition, patients with coronary artery disease are given treatment to maintain their hemoglobin concentrations at a minimum of 100 g/l (45). In each case, prophylactic blood transfusions may decrease the risk of developing CIN and the risk of mortality, in particular in anemic patients at risk of myocardial infarction.

In the present study, no severe clinical manifestations in the patients with CIN were detected, such as acute renal failure requiring dialysis or mortality resulted from CIN. In general, levels of serum creatinine typically peaked at 3-5 days following exposure to contrast agents, and returned to the baseline, or near baseline, level within 1-3 weeks following adequate hydration (46).

Several limitations of the present study should be noted, firstly that it is a retrospective study. Secondly, the renal function of patients was only assessed based on the increase in serum creatinine; no other indicators, such as glomerular filtration rate, were used. Thirdly, the present study included patients with multi-vessel and single coronary artery diseases, and the former may necessitate the use of higher volumes of contrast media. Finally, the hemoglobin level in populations is known to vary with altitude (47). The current study was performed in Southeast China, a region of low altitude. Thus, the results of the present study should be reviewed with caution.

In conclusion, patients with low levels of hemoglobin, including those with normal renal function, are at a higher risk of developing CIN. Therefore, the level of hemoglobin should be closely monitored in patients with low hemoglobin prior to administration of contrast media, particularly in those with hemoglobin levels below the cut-off point and at risk of developing CIN.

## Acknowledgements

The present study was supported by grants from the Wenling Foundation of Science and Technology (no. 2011WLCB0109 and 2014C311051), the Natural Science Foundation of China (no. 81100993 and 81300311), the Zhejiang Natural Science Foundation (no. LY12H03001 and LQ13H280002) and the Research Development Fund of Wenzhou Medical University (no. QTJ15001).

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