Predictors of contrast-induced acute kidney injury in patients with coronary artery disease receiving contrast agents twice within 30 days

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Abstract

Background: None of study mentioned about contrast-induced acute kidney injury (CI-AKI) in people who have received contrast agents twice within in a short period of time. This study is trying to identify the predictors.

Methods: We enrolled 607 patients between Oct. 2010 and Jul. 2015 who received contrast agents twice within 30 days in the Department of Cardiology of the General Hospital of Shenyang Military Region. The primary outcome was CI-AKI within 72 h after contrast agent exposure. Patients were divided into groups A (n = 559) and group B (n = 48) according to whether CI-AKI occurred after the second agent.

Results: Patients in group B (CI-AKI occurred after the second agent) had a more rapid heart rate and more usage of diuretics and digitalis. In group B, CI-AKI occurred more frequently after the first agent. Multivariate logistic regression showed that diuretic (P = 0.006) and intra-aortic balloon pump (IABP) usage (P = 0.012) were independent predictors of CI-AKI after the first agent. Angiotensin-converting enzyme inhibitor/Angiotensin II receptor antagonist (ACEI/ARB) usage (P = 0.039), IABP usage (P = 0.040) and CI-AKI occurring after administration of the first agent (P = 0.015) were independent predictors of CI-AKI after the second. Furthermore, dividing the patients into tertiles of the time interval between the two agents showed that CI-AKI occurred more frequently when the second agent was administered within 1–3 days after the first exposure than within 4–6 days (12.4% vs. 5.0%, P = 0.008) or ≥7 days (12.4% vs. 6.4%, P = 0.039).

Conclusions: Diuretic and IABP usage are independent predictors of CI-AKI following exposure to a first contrast agent. The major predictors of CI-AKI after exposure to a second agent are time since the first contrast exposure, ACEI/ARB usage, and IABP usage. More importantly, a three-day interval between the two agents is associated with a higher incidence of CI-AKI following the second administration.

Keywords: Predictors, Contrast-induced acute kidney injury, Coronary artery disease
Background

Contrast-induced acute kidney injury (CI-AKI) is a familiar complication experienced by patients with coronary artery disease (CAD) who are administered iodine-containing contrast agents for procedures such as coronary angiography (CAG) and percutaneous coronary intervention (PCI) [1–3]. CI-AKI has been proven to be associated with risk indices of longer hospitalization and short- and/or long-term mortality [2, 4, 5]. The incidence of CI-AKI is approximately 0.6–2.3% [6]. However, this value varies depending on the presence of risk factors, and several clinical predictors of CI-AKI have been introduced [7, 8]. Additionally, CI-AKI has been linked with a worse clinical outcome in patients with acute coronary syndrome (ACS) [5, 8–10]. Well-established risk factors of CI-AKI include diabetes, congestive heart failure, acute hypotension, advanced age, ST-elevation myocardial infarction (STEMI), volume depletion, the amount of contrast administered, the type of contrast media, and the simultaneous use of nephrotoxic medications in unselected patients after CAG or PCI [7, 11, 12]. However, those studies mainly focused on the effect of a one-time exposure to a contrast agent on in-hospital or long-term endpoints [5, 8, 9].

It is becoming more common for patients with CAD to receive a contrast agent two or more times (CAG or PCI) because of delay-PCI, rescue-PCI or other reasons. The aim of our investigation was to evaluate predictors of the development of CI-AKI in patients who received contrast agents twice within 30 days and the association between CI-AKI and adverse clinical outcomes.

Methods

Study population

This was a single-center, retrospective, observational study. All research adhered to the tenets of the Declaration of Helsinki, and compliance was maintained throughout the study. The subjects were recruited from the cardiovascular catheterization database of the General Hospital of Shenyang Military Region between Oct. 2010 and Jul. 2015. The total number of patients who underwent CAG or PCI was 23,444. Of these patients, 607 received contrast agents twice within a 30-day period. All patients provided written informed consent. All experimental and operational procedures were performed using standard interventional techniques. Cardiogenic shock (CS) patients were excluded. CS is defined below. Patients were divided into two groups according to whether CI-AKI occurred following exposure to the second agent: group A (n = 559), no occurrence of CI-AKI following the second agent, and group B (n = 48), occurrence of CI-AKI following the second agent.

Definitions

The primary outcome was CI-AKI after any of the contrast agents. CI-AKI was diagnosed based on the Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease/Acute Kidney Injury Network (RIFLE/AKIN) criteria, which were defined as a serum creatinine level increase of 25% or creatinine 0.5 mg/dl or more above baseline within 72 h after the administration of the contrast agent [13, 14]. The estimated glomerular filtration rate (eGFR) was calculated using the equation from the Modification of Diet in Renal Disease formula: eGFR = 175 × serum creatinine−1.154 × age−0.203 × (0.742, if female) [15]. Chronic kidney disease (CKD) was defined as an eGFR < 60 ml/(min·1.73 m²) for at least 3 months [16]. Serum creatinine was measured before the procedure and daily for 3 days after the administration of the contrast agent. ACS was defined according to the guidelines of the European Society of Cardiology (ESC) [17]. Patients at high risk of CI-AKI after exposure to any of the contrast agents routinely received intravenous hydration treatment with saline solution administered at 1 ml/(kg·h) for 12 h after exposure to the contrast agent. Anemia was defined as hemoglobin (Hb) of less than 12 g/dl in females and 13 g/dl in males according to the World Health Organization’s recommendation [18]. Positive cardiac markers at admission were defined as an elevated serum troponin I (cut-off of 0.15 ng/ml) and/or a creatine kinase-myocardial band (CK-MB) (cut-off of 24 U/L). ST elevation on the admission electrocardiogram (ECG) was defined as recommended by the ESC guidelines [19]. CS was defined as a systolic blood pressure of less than 85 mmHg with evidence of decreased organ perfusion caused by severe left ventricular dysfunction, right ventricular infarction or mechanical complications of the infarction [9].

Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD) or the median, as appropriate, and categorical variables are given as percentages (%). The t-test or Mann-Whitney U test was used to compare continuous variables between two groups, and one-way ANOVA was used to compare categorical variables between groups. The chi-squared test was used to compare the rates of outcomes. Basic data were analyzed by using IBM SPSS version 20.0. Differences in demographic variables were evaluated using the chi-squared test. Non-normally distributed continuous variables, presented as medians and interquartile ranges, were analyzed using the Wilcoxon rank-sum test. Logistic regression analysis was used to calculate odds ratios for the comparison of CI-AKI rates between groups. Multivariate analysis for CI-AKI included the results with values of P < 0.05 in the univariate analysis or those that could potentially
affect the clinical outcome according to our experience. Survival analysis was used to compare patients who developed CI-AKI and those who did not develop CI-AKI following administration of the second agent using the Kaplan-Meier estimator. All P values were two tailed, and statistical significance was defined by a P value < 0.05.

Results
The 607 consecutive patients exposed to contrast agents twice within 30 days and who had complete clinical data were separated into two groups (A and B) according to whether CI-AKI occurred following the second exposure. Forty-eight (7.9%) patients developed CI-AKI after the second administration. Baseline characteristics, laboratory results and medications for the two groups are listed in Table 1. Patients in group B exhibited a faster in-hospital heart rate (81.4 ± 17.3 beat/min vs. 76.4 ± 14.1 beat/min, P = 0.022). Diuretics (56.3% vs. 37.6%, P = 0.011) and digitalis (35.4% vs. 18.4%, P = 0.005) were also used more frequently in group B. The other variables did not differ significantly between the two groups.

A review of the procedural details revealed that there was no significant difference between the two groups in the operative approach or the amount of contrast media used during the procedure. In addition, the number of stent implantations and lesions matched well. Nonetheless, CI-AKI occurred more frequently after exposure to the first contrast agent in group B (31.3% vs. 7.3%, P < 0.001). Furthermore, the maximal serum creatinine level was higher in group B than in group A following exposure to the second agent (100.1 ± 27.3 μmol/L vs. 76.6 ± 27.7 μmol/L, P < 0.001, Table 2).

Binary logistic regression was performed to identify predictors of CI-AKI in patients who received a contrast agent twice. In the multivariate regression model, the independent predictors for the occurrence of CI-AKI after the first contrast agent were diuretic (P = 0.006) and IABP usage (P = 0.012, Table 3), while for the second agent, CI-AKI indices from the multivariate regression model revealed that the independent predictors were the time interval between exposure to the two agents (P = 0.037), ACEI/ARB usage (P = 0.039), IABP usage (P = 0.040) and the occurrence of CI-AKI following the first agent (P = 0.015, Table 4).

We separated patients by tertiles of the interval between the two agents: 1–3 days, 4–6 days and ≥7 days between exposures. The incidence of CI-AKI following the second agent was significantly higher in the 1–3-day group than 4–6-day group (12.4% vs. 5.0%, P = 0.008) and ≥7 day group (12.4% vs. 6.4%, P = 0.039, Fig. 1).

All patients had complete clinical follow-up data. The median follow-up duration was 37 months (interquartile range: 23 to 61). The incidence of all-cause death was similar between the two groups (3.8% vs. 4.2%, P = 0.426). Total major adverse cardiovascular events (MACE) appeared in 51 (9.1%) group A patients and 6 (12.5%) group B patients (P = 0.438). Among these participants, cardiac death occurred in 22 patients (group A vs. group B = 3.4% vs. 4.2%, P = 0.154) during the follow-up period. Only 3 patients (group A) had a myocardial infarction during the follow-up period. The incidence of in-stent restenosis was also not significantly different between the two groups (5.0% vs. 6.3%, P = 0.728, Table 5). After adjusting for clinically and statistically relevant covariates, the incidence of MACE and all-cause death was higher in group B, although this difference was not significant (Fig. 2).

Discussion
In the present study, we aimed to investigate the possible predictors of CI-AKI in patients who received a contrast agent twice within 30 days. The major findings of this study are as follows: 1) diuretic (P = 0.006) and IABP usage (P = 0.012) were strongly associated with the development of CI-AKI following administration of the first contrast agent; 2) the time interval between the two procedures (P = 0.037), ACEI/ARB usage (P = 0.039), IABP usage (P = 0.040) and the occurrence of CI-AKI after the first procedure (P = 0.015) were independent predictors of CI-AKI following exposure to the second contrast agent; and 3) if the time interval between the two procedures was 3 days or less, then CI-AKI following the second contrast agent was more likely.

The main finding of the present study is the identification of several independent risk factors for CI-AKI in patients receiving a contrast agent twice within a short period of time. Some of the established risk factors have also been corroborated in our study, such as diuretics and IABP usage [20, 21]. We found that IABP usage could also increase the incidence of CI-AKI after the second contrast agent. The reason for this finding may be similar to those reported in previous literature. Those findings mainly relate to the nature of intra-arterial injection, the high volume of the contrast, the patients’ advanced age, and the severity of the patients’ illness, such as a greater number of comorbid conditions, more advanced vascular disease, hypertension, and diabetes [22, 23].

The relationship between ACEI/ARB and CI-AKI is still controversial. Some investigators have pointed out that the use of ACEI/ARB may protect the kidneys against the effects of CI-AKI [24, 25]. Recently, Duan et al. [26] proposed that ACEIs can prevent CI-AKI. Nonetheless, opposing results have been published over the past few years. For example, Kiski et al. [27] found that patients taking ACEIs/ARBs developed CI-AKI significantly more often within 72 h after contrast media.
### Table 1 Baseline patient characteristics in two groups

| Item                                      | Group A (n = 559) | Group B (n = 48) | P value |
|-------------------------------------------|-------------------|------------------|---------|
| Age (year, x ± s)                         | 60.2 ± 11.0       | 61.5 ± 12.7      | 0.438   |
| Female [n(%)]                             | 121 (21.6)        | 14 (29.1)        | 0.229   |
| Weight (kg, x ± s)                        | 71.7 ± 11.7       | 72.1 ± 11.7      | 0.821   |
| Height (cm, x ± s)                        | 169.9 ± 6.6       | 170.3 ± 6.7      | 0.699   |
| BMI (kg/m², x ± s)                        | 24.8 ± 3.6        | 24.9 ± 3.7       | 0.930   |
| Current smoker [n(%)]                     | 288 (51.5)        | 27 (56.2)        | 0.529   |
| Current alcohol [n(%)]                    | 180 (32.2)        | 14 (29.1)        | 0.665   |
| STEMI [n(%)]                              | 196 (35.0)        | 22 (45.8)        | 0.136   |
| Hypertension [n(%)]                       | 303 (54.2)        | 33 (68.7)        | 0.051   |
| Diabetes [n(%)]                           | 132 (23.6)        | 16 (33.3)        | 0.132   |
| CKD [n(%)]                                | 34 (6.1)          | 6 (12.5)         | 0.119   |
| Stroke [n(%)]                             | 53 (9.5)          | 8 (16.7)         | 0.130   |
| Cancer [n(%)]                             | 4 (0.7)           | 0                | 1.000   |
| Peripheral vascular disease [n(%)]        | 7 (1.3)           | 2 (4.2)          | 0.109   |
| Ulcer [n(%)]                              | 58 (10.4)         | 4 (8.3)          | 0.807   |
| NYHA class II-III [n(%)]                  | 109 (19.5)        | 15 (31.3)        | 0.053   |
| SBP (mmHg, x ± s)                         | 133.9 ± 21.9      | 136.8 ± 22.4     | 0.379   |
| DBP (mmHg, x ± s)                         | 79.3 ± 13.4       | 80.85 ± 13.5     | 0.426   |
| HR (beat/min, x ± s)                      | 76.4 ± 14.1       | 81.4 ± 17.3      | 0.022   |
| Basic-Scr (μmol/L, x ± s)                | 77.4 ± 25.0       | 75.1 ± 24.5      | 0.548   |
| Basic-eGFR [ml/(min·1.73m²), x ± s]       | 108.4 ± 41.5      | 110.0 ± 43.0     | 0.908   |
| BUN (mmol/L, x ± s)                       | 5.9 ± 1.9         | 6.1 ± 1.3        | 0.638   |
| K⁺ (mmol/L, x ± s)                        | 4.1 ± 0.4         | 4.2 ± 0.3        | 0.243   |
| Na⁺ (mmol/L, x ± s)                       | 140.1 ± 3.4       | 139.6 ± 3.0      | 0.391   |
| PLT (×10⁹/L, x ± s)                       | 208.8 ± 55.8      | 209.5 ± 55.4     | 0.943   |
| WBC (×10⁹/L, x ± s)                       | 8.3 ± 3.1         | 8.3 ± 2.8        | 0.995   |
| Hb (g/L, x ± s)                           | 137.9 ± 24.1      | 136.2 ± 17.4     | 0.671   |
| TC (mmol/L, x ± s)                        | 4.2 ± 1.3         | 4.1 ± 1.0        | 0.819   |
| TG (mmol/L, M(Q₁, Q₃))²                   | 1.48 (1.13,1.72)  | 1.44 (0.72,1.98) | 0.367   |
| ALT (mmol/L, M(Q₁, Q₃))²                  | 26.00 (13.81)     | 24.00 (9.63)     | 0.975   |
| AST (mmol/L, M(Q₁, Q₃))²                  | 25.00 (7.76)      | 23.00 (4.67)     | 0.250   |
| ALB (mmol/L, x ± s)                       | 33.2 ± 20.5       | 35.3 ± 15.5      | 0.718   |
| HDL-C (mmol/L, x ± s)                     | 1.2 ± 0.4         | 1.0 ± 0.3        | 0.684   |
| LDL-C (mmol/L, x ± s)                     | 2.4 ± 1.0         | 2.4 ± 0.9        | 0.790   |
| Glucose (mmol/L, x ± s)                   | 6.6 ± 2.9         | 7.2 ± 3.4        | 0.337   |
| CK [U/L, M(Q₁, Q₃)]²                      | 137.00 (27.31,452.50) | 108.00 (45.79,168.75) | 0.303 |
| CK-MB [U/L, M(Q₁, Q₃)]²                   | 17.00 (7.14,22.75) | 17.00 (6.34,16.75) | 0.936 |
| TNT (μg/L, M(Q₁, Q₃))²                    | 0.05 (0.01,0.523) | 0.05 (0.01,0.162) | 0.241 |
| NT-proBNP [μg/L, M(Q₁, Q₃)]²              | 83.00 (12.00,1085.00) | 140.00 (21.00,2050.00) | 0.236 |
| LV (mm, x ± s)                            | 48.8 ± 6.4        | 49.8 ± 5.8       | 0.687   |
| EF (% , x ± s)                            | 58.9 ± 10.7       | 57.6 ± 11.6      | 0.730   |
| Medicine care [n(%)]                      |                   |                  |         |
| Diuretics                                 | 210 (37.6)        | 27 (56.3)        | 0.011   |
| CCB                                       | 231 (41.3)        | 21 (43.8)        | 0.743   |
administration. This observation is consistent with our results, which showed that the use of ACEIs/ARBs was associated with an increased incidence of CI-AKI following exposure to the second contrast agent.

We also found that if patients developed CI-AKI following the first procedure, then they were more likely to develop CI-AKI after the second procedure. It is well known that the mechanism of CI-AKI is mainly caused by the toxic properties of the contrast media, such as osmolality, viscosity, and ionic strength. The cytotoxicity of contrast agents is probably caused by iodine and leads to apoptosis and cell death of both endothelial and tubular cells [28]. Therefore, in patients who have recently developed one episode of CI-AKI, contrast toxicity and other factors may affect kidney function, increasing the likelihood of more frequent episodes of CI-AKI following the second exposure.

In the present study, we newly identified that the time interval between two exposures to contrast agents is an independent predictor of CI-AKI following the second procedure. Further analysis showed that the incidence of CI-AKI during the second peri-operative period was significantly higher if the second exposure occurred within 3 days rather than 4–6 days or ≥7 days. In the 2015 ESC congress, Park et al. [29] reported a similar result when evaluating the safe time interval between exposure to multidetector computed tomography (MDCT) and coronary

### Table 2: Agent procedural characteristics in two groups

| Item                    | Group A (n = 559) | Group B (n = 48) | P value |
|-------------------------|-------------------|-----------------|---------|
| TRI                     | 469 (83.9)        | 40 (83.3)       | 0.918   |
| ACEI/ARB                | 444 (79.4)        | 34 (70.8)       | 0.162   |
| Statins                 | 366 (65.5)        | 37 (77.1)       | 0.102   |
| Digitalis               | 103 (18.4)        | 17 (35.4)       | 0.005   |

Group A No CI-AKI from second agent, Group B CI-AKI from second agent, TRI Trans-radial intervention, CV Contrast volume, LM Left main, SYNTAX Synergy between percutaneous coronary intervention with Taxus and cardiac surgery

*Means non-normally distributed continuous variables*
revascularization regarding the risk of CI-AKI. Their study pointed out that CI-AKI was more frequent in the earlier time interval in the PCI group. Furthermore, multivariate analysis identified a short interval between MDCT and PCI as a unique independent predictor of CI-AKI (≤ 2 days vs. > 14 days: \( HR = 2.37, 95\% \, CI: \, 1.105–5.098, \, P = \, 0.018; \) 3–14 days vs. > 14 days: \( HR = 2.07, 95\% \, CI: \, 0.960–4.445, \, P = \, 0.064). Some articles have reported that serum creatinine will usually peak 2–3 days following injection of a contrast agent and then slowly return to baseline within 14 days [30, 31]. Our result may have been because a repeat injection of contrast agent within 3 days (72 h) of the first exposure occurred at the time of peak renal

### Table 3 Regression analysis for CI-AKI predictors of the first agent

| Variable           | Univariate analysis | Multivariate analysis |
|--------------------|---------------------|-----------------------|
|                    | \( P \) value       | \( OR \)               | \( 95\% \, CI \) | \( P \) value |
| Female             | 0.854               | 1.026                 | 0.424–2.484 | 0.954 |
| NYHA Class II-III  | 0.004               | 1.326                 | 0.542–3.248 | 0.536 |
| Hypertension       | 0.626               | 1.671                 | 0.736–3.796 | 0.220 |
| Diabetes           | 0.276               | 1.179                 | 0.483–2.876 | 0.718 |
| Diuretics          | < 0.001             | 3.761                 | 1.462–9.675 | 0.006 |
| CCB                | 0.228               | 0.269                 | 0.086–1.383 | 0.240 |
| \( \beta \)-RB     | 0.715               | 0.399                 | 0.157–1.011 | 0.053 |
| ACEI/ARB           | 0.757               | 0.575                 | 0.240–1.377 | 0.214 |
| Statins            | 0.518               | 0.643                 | 0.097–3.304 | 0.390 |
| Digitalis          | 0.010               | 1.588                 | 0.608–4.149 | 0.345 |
| IABP               | < 0.001             | 4.245                 | 1.378–13.083 | 0.012 |
| LM lesion          | 0.716               | 0.564                 | 0.256–1.241 | 0.155 |
| Age                | 0.381               | 1.000                 | 0.965–1.035 | 0.983 |
| Basic SYNTAX score | 0.078               | 0.996                 | 0.946–1.047 | 0.861 |

**NYHA** New York Heart Association, **CCB** Calcium channel blocker, **\( \beta \)-RB** \( \beta \)-receptor blocker, **ACEI** Angiotensin-converting enzyme inhibitor, **ARB** Angiotensin II receptor antagonist, **IABP** Intra-aortic balloon pump, **LM** Left main, **SYNTAX** Synergy between percutaneous coronary intervention with Taxus and cardiac surgery, CI-AKI Contrast-induced acute kidney injury

### Table 4 Regression analysis for CI-AKI predictors after second agent

| Variable           | Univariate analysis | Multivariate analysis |
|--------------------|---------------------|-----------------------|
|                    | \( P \) value       | \( OR \)               | \( 95\% \, CI \) | \( P \) value |
| Interval time      | 0.033               | 1.170                 | 1.980–2.370 | 0.037 |
| Female             | 0.232               | 1.460                 | 0.660–3.226 | 0.350 |
| NYHA class II-III  | 0.056               | 1.381                 | 0.576–3.309 | 0.469 |
| Hypertension       | 0.064               | 2.107                 | 0.929–4.774 | 0.074 |
| Diabetes           | 0.135               | 1.296                 | 0.582–2.888 | 0.526 |
| Diuretics          | 0.012               | 1.268                 | 0.489–3.288 | 0.625 |
| CCB                | 0.743               | 1.329                 | 0.601–2.939 | 0.482 |
| \( \beta \)-RB     | 0.918               | 0.698                 | 0.277–1.759 | 0.446 |
| ACEI/ARB           | 0.166               | 0.428                 | 0.191–0.958 | 0.039 |
| Statins            | 0.106               | 4.203                 | 0.809–21.846 | 0.088 |
| Digitalis          | 0.006               | 1.291                 | 0.453–3.677 | 0.632 |
| IABP               | 0.001               | 3.302                 | 1.055–10.335 | 0.040 |
| LM lesion          | 0.164               | 0.880                 | 0.356–2.177 | 0.782 |
| Age                | 0.438               | 0.996                 | 0.963–1.031 | 0.838 |
| Basic SYNTAX score | 0.083               | 1.006                 | 0.952–1.063 | 0.838 |
| CI-AKI post-first agent | < 0.001 | 3.454               | 1.278–9.333 | 0.015 |

**NYHA** New York Heart Association, **CCB** Calcium channel blocker, **\( \beta \)-RB** \( \beta \)-receptor blocker, **ACEI** Angiotensin-converting enzyme inhibitor, **ARB** Angiotensin II receptor antagonist, **IABP** Intra-aortic balloon pump, **LM** Left main, **SYNTAX** Synergy between percutaneous coronary intervention with Taxus and cardiac surgery, CI-AKI Contrast-induced acute kidney injury
toxicity caused by the previous agent. Therefore, such a strategy of repeat procedures may expose kidneys to a higher risk of CI-AKI.

Other factors, such as diabetes and left main coronary artery lesions, have been reported to be strong risk factors for CI-AKI in previous studies [2, 32]. Though the results of our multivariate analysis did not find similar correlations, trends were evident for several of these factors. In addition, the lack of significant associations may be related to the small sample size of group B.

Recent studies have demonstrated that for patients who develop CI-AKI following exposure to a contrast agent, the in-hospital and long-term adverse clinical outcomes can be attributed to cardiovascular instability and the resulting complications [2, 5, 33]. In our study, the clinical adverse events were more numerous for patients who developed CI-AKI after the second contrast agent. These findings seem to be consistent with those of previous studies [34, 35]. However, patients who developed CI-AKI after the second contrast agent did not have a significantly worse clinical prognosis during the follow-up period. This finding might be explained by the fact that some patients in group A developed CI-AKI after the first agent, while some in group B did not, which could have affected the results. The small sample size of patients receiving contrast media twice may also have impacted death or MACE incidence in this study.

Our study has several limitations. First, this study used a nonrandomized, retrospective, single-center design, which may have significantly affected the results due to confounding factors. Second, we excluded some patients whose information regarding contrast media usage and serum creatinine levels during the procedures was lost, which could potentially result in serious selection bias. Additionally, atrial fibrillation has been notoriously recognized as a predictor of poor prognostic outcomes, but we have not analyzed arrhythmia types such as atrial fibrillation or any others. We have added this to the limitation section, and will analyze arrhythmia in future papers.

Table 5 Clinical follow-up after contrast medium administration [n(%)]

| Variable                      | Group A (n = 559) | Group B (n = 48) | P value |
|-------------------------------|------------------|------------------|---------|
| All cause death               | 21 (3.8)         | 3 (4.2)          | 0.426   |
| MACE                          | 51 (9.1)         | 6 (12.5)         | 0.438   |
| Cardiac death                 | 19 (3.4)         | 3 (4.2)          | 0.154   |
| Myocardial infarction         | 3 (0.5)          | 0                | 1.000   |
| In-stent restenosis           | 28 (5.0)         | 3 (6.3)          | 0.728   |
| Stent thrombosis              | 1 (0.2)          | 0                | 1.000   |

Group A No CI-AKI from 2nd agent, Group B CI-AKI from 2nd agent, MACE Major Adverse Cardiovascular Events

Fig. 1 CI-AKI occurrence after the 2nd agent by tertile of the interval between the two contrast agent exposures
Finally, in the receiver operator characteristic curve analysis, our cut-off value for predicting the development of CI-AKI in patients who received a contrast agent twice within 30 days had a slightly low sensitivity. This may be caused by the small sample size. Nevertheless, our multivariate analysis showed that the time interval between administration of the two contrast agents was one of the major predictors for developing CI-AKI, even after adjusting for various confounding factors. Further multicenter, large-scale and randomized studies may be needed to confirm this observation.

Conclusions
In conclusion, there are several major predictors of CI-AKI in patients who receive a contrast agent twice within 30 days. Diuretic and IABP usage are independent predictors of CI-AKI following exposure to the first contrast agent. The major predictors of CI-AKI after the second contrast agent are the time interval between exposures, ACEI/ARB usage, and IABP usage. Furthermore, if the interval between two procedures is 3 days or less, then CI-AKI following the second administration of a contrast agent is more likely.

Abbreviations
ACS: Acute coronary syndrome; ACEI: Angiotensin-converting enzyme inhibitor; ALB: Albumin; ALT: Alanine aminotransferase; ARB: Angiotensin II receptor antagonist; AST: Aspartate aminotransferase; BMI: Body mass index; β-RB: β-receptor blocker; BUN: Blood urea nitrogen; CAD: Coronary artery disease; CAG: Coronary angiography; CCB: Calcium channel blocker; CI-AKI: Contrast-induced acute kidney injury; CK: Creatine kinase; CKD: Chronic kidney disease; CK-MB: Creatine kinase-myocardial band; CS: Cardiogenic shock; CV: Contrast volume; DBP: Diastolic blood pressure; ECG: Electrocardiogram; EF: Ejection fraction; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; HDL-C: High-density lipoprotein cholesterol; HR: Heart rate; IABP: Intra-aortic balloon pump; LDL-C: Low-density lipoprotein cholesterol; LM: Left main; LV: Left ventricular; MACE: Major adverse cardiovascular events; MDCT: Multidetector computed tomography; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention; PLT: Platelets; SBP: Systolic blood pressure; Scr: Serum creatinine; STEMI: ST-segment elevation myocardial infarction; SYNTAX: Synergy between percutaneous coronary intervention with Taxus and cardiac surgery; TC: Total cholesterol;
TG: Triglycerides; TNT: Troponin T; TRI: Trans-radial intervention; WBC: White blood cells

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The material has not otherwise been presented or published.

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XZW, QMJ and XZ performed the patient surgeries. XZ and YLH carried out the statistical analysis. XZ collected the data. CHG participated in the design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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All patients or their relatives provided informed consent, and the study was approved by the ethical committee of General Hospital of Shenyang Military Region.

Consent for publication
All authors consent to publication in Military Medical Research.

Competing interests
The authors declare that they have no competing interests.

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