Nomogram for contrast-induced acute kidney injury in patients with chronic kidney disease undergoing coronary angiography in China: a cohort study

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ABSTRACT

Objectives To establish a nomogram for contrast-induced acute kidney injury (CI-AKI) risk assessment among patients with chronic kidney disease (CKD) undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI).

Design Prospective observational cohort study.

Setting Southern China.

Interventions None.

Participants 643 consecutive patients with CKD (defined as estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease formula <60 mL/min/1.73 m²) were enrolled.

Outcome measures The end point was CI-AKI defined as serum creatinine elevation ≥0.5 mg/dL or 25% from baseline within the first 48–72 hours following contrast exposure. Predictors of CI-AKI were selected by multivariable logistic regression and stepwise approach. A nomogram based on these predictors was constructed and compared with the classic Mehran Score. For validation, a bootstrap method (1000 times) was performed.

Results The nomogram including age, weight, heart rate, hypotension, PCI and β-blocker demonstrated a better predictive value than the classic Mehran Score (area under the curve: 0.78 vs 0.71, p=0.024), as well as a well-fitted calibration curve (χ²=12.146, p=0.145). Validation through the bootstrap method (1000 times) also indicated a good discriminative power (adjusted C-statistic: 0.76).

Conclusions With fewer predictors and higher discriminative power, the present nomogram may be a simple and reliable tool to identify patients with CKD at risk of CI-AKI, whereas further external validations are needed.

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) is one of the most common complications following coronary angiography (CAG) or percutaneous coronary intervention (PCI) and is associated with worse prognosis including higher mortality and accelerated progression of underlying chronic kidney disease (CKD). The 2018 European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines on myocardial revascularisation recommended that all patients should be assessed for the risk of CI-AKI while having contrast exposure.

Various prediction models are available by now. A traditional risk score including eight variables established by Mehran et al in 2004 is one of the most common prediction models for CI-AKI. Although it is classic, the Mehran Score is too complicated to be applied in routine clinical practice. Moreover, the discriminative power of the Mehran Score is relatively low (C-statistic 0.67). Silver et al conducted a meta-analysis on a CI-AKI prediction model in 2015, and found that most predictive models in clinical use have only modest ability (C statistic of 0.7–0.8). Another meta-analysis conducted by Allen et al failed to find the most suitable model for clinical practice, and evaluating the clinical impact of prediction models for CI-AKI before they can be broadly recommended was still needed.

Patients complicated with CKD are at high risk of CI-AKI. However, after a systematic research, few prediction models were identified for such patients. Therefore, we...
conducted this study to establish a nomogram for CI-AKI risk assessment among patients with CKD undergoing CAG/PCI.

METHODS

Patients

Between January 2010 and October 2012, consecutive patients aged ≥18 years with CKD (defined as estimated glomerular filtration rate (eGFR) calculated by Modification of Diet in Renal Disease formula <60 mL/min/1.73 mm²) from a prospective observation cohort (PREdictive Value of COntrast voluMe to creatinINe Clearance Ratio, NCT01400295) who underwent CAG/PCI in Guangdong Provincial Peoples Hospital were enrolled. The exclusion criteria were pregnancy, lactation, malignancy, and no use of isotonic saline for hydration. All eligible patients enrolled were followed up at 1 month, 6 months and every 1 year after enrolment until April 2019.

Patient and public involvement

Patients and the public were not involved.

CAG and laboratory examination

The procedure was performed by interventional cardiologists according to published guidelines, institutional policy and routine practice. Baseline characteristics, angiographic data and medications were prospectively defined and have been reported in a previous study. Left ventricular ejection fraction (LVEF) was calculated through the biplane modified Simpson’s rule by two-dimensional echocardiography. Serum creatinine (Scr) was measured for all patients at admission and at 1, 2 and 3 days after the procedure using the Jaffe method. All the patients included in this study provided written informed consent.

End point and definitions

The end point of this study was CI-AKI defined as an Scr elevation ≥0.5 mg/dL or 25% from baseline within the first 48–72 hours following contrast exposure. Hypoaalbuminaemia was defined as serum albumin <35 g/L. The definitions of anaemia and hypotension were the same as those in the Mehran Score. Patients were also divided into four CKD stages according to the guidelines (CKD G3a: eGFR: 45–59 mL/min/1.73 mm²; CKD G3b: eGFR: 30–44 mL/min/1.73 mm²; CKD G4: eGFR: 15–29 mL/min/1.73 mm²; CKD G5: eGFR<15 mL/min/1.73 mm²). All eligible patients enrolled were followed up at 1 month, 6 months and every 1 year after enrolment until April 2019.

Statistical analysis

Individual points of Mehran Score were calculated as previously reported. Continuous variables were compared through an unpaired, two-tailed t test and expressed as mean±SD, or compared through the Wilcoxon rank-sum test and expressed as median±IQR. Categorical variables were compared using the χ² test or Fisher’s exact test and expressed as a percentage. Multivariable Cox proportional hazards regressions adjusted for risk factors regarding long-term prognosis were fitted to explore the impact of CI-AKI on long-term prognosis. Kaplan-Meier analysis was used to count the cumulative mortality, and log-rank test was used to assess differences between curves.

Variables that were imbalanced between groups or clinically important, such as risk factors of the traditional Mehran Score, were candidates for univariable logistic analysis. Significant predictors from the univariable logistic analysis were then included in the multivariable logistic analysis to fit a prediction model. A backward stepwise approach was performed to create a reduced model by successively removing non-significant covariates (p>0.1) until all the remaining predictors are statistically significant. Collinearity between variables was also evaluated. A nomogram was then formulated based on the results and by using the rms package of R. To form the nomogram, each regression coefficient in the multivariable logistic regression was proportionally converted into a 0–100-point scale. Variables with the highest β coefficient (absolute value) was assigned 100 points. The points are added across each variable to calculate the total points, which are finally converted to predicted probabilities. The performance of the nomogram was assessed using the area under the receiver operating characteristic (ROC) curve and concordance C-statistic for discriminative ability and calibration with 1000 bootstrap samples to decrease the overfit bias. Calibration was assessed using the Hosmer-Lemeshow test. After the model was set up, we calculated individual scores for each patient, which was used to estimate the individual risk. At the same time, we also used these scores to build up a ROC curve. The cut-off score to identify patients at risk of CI-AKI was then derived from the ROC curve. The tendency test of the risk score was conducted by the Cochran-Armitage trend test. Area under curve comparison between the nomogram and the Mehran Score was performed using DeLong’s test. We also calculated the net reclassification improvement (NRI) at the threshold for CI-AKI risk derived by Mehran et al (7.5% and 26.1%). NRI calculation was conducted using the nricens package. Missing data were not imputed. In all analyses, p<0.05 was considered statistically significant. All analyses were conducted with R software (V.3.6.2; R Foundation for Statistical Computing, Vienna, Austria) and SPSS (V.26.0).

RESULTS

Baseline characteristic

The details of the included patients are listed in table 1. Among the 643 patients with CKD, less than a third were female (28.15%). The mean age was 69.88±9.67 years, and the mean Scr was 145.39±70.94 μmol/L.
## Table 1  Baseline characteristics

| Variables                        | Total (n=643) | Missing data (%) | CI-AKI (n=96) | non-CI-AKI (n=547) | P value |
|----------------------------------|---------------|------------------|---------------|--------------------|---------|
| Age, years                       | 69.88±9.67    | 0 (0)            | 74.47±8.45    | 69.07±9.65         | <0.001  |
| Age >75 years, n (%)             | 234 (36.39)   | 0 (0)            | 54 (56.25)    | 180 (32.91)        | <0.001  |
| Female sex, n (%)                | 181 (28.15)   | 0 (0)            | 37 (38.54)    | 144 (26.33)        | 0.014   |
| Weight, kg                       | 63.63±10.27   | 8 (1.24)         | 60.37±8.97    | 64.21±0.24         | <0.001  |
| SBP, mm Hg                       | 129.61±23.81  | 2 (0.31)         | 128.16±28.67  | 129.87±22.87       | 0.579   |
| DBP, mm Hg                       | 74.16±12.48   | 2 (0.31)         | 73.47±13.95   | 74.28±12.21        | 0.593   |
| HR, bpm                          | 76.58±15.12   | 3 (0.47)         | 81.43±18.31   | 75.72±14.33        | 0.004   |
| **Medical history**              |               |                  |               |                    |         |
| Chronic heart failure, n (%)     | 468 (73.01)   | 2 (0.31)         | 77 (80.21)    | 391 (71.74)        | 0.085   |
| Hypotension, n (%)               | 25 (3.91)     | 4 (0.62)         | 12 (12.77)    | 13 (2.39)          | <0.001  |
| %                                | 53.52±13.63   | 74 (11.51)       | 51.20±13.08   | 53.95±13.69        | 0.072   |
| LVEF <40%, n (%)                 | 100 (17.57)   | 18 (20.22)       | 82 (17.08)    |                    | 0.475   |
| Hypertension, n (%)              | 475 (73.87)   | 0 (0)            | 74 (77.08)    | 401 (73.31)        | 0.438   |
| Hyperlipidaemia, n (%)           | 85 (13.22)    | 0 (0)            | 14 (14.58)    | 71 (12.98)         | 0.669   |
| Hypoaalbuminaemia, n (%)         | 356 (55.32)   | 98 (15.24)       | 53 (75.14)    | 303 (63.79)        | 0.05    |
| Anaemia, n (%)                   | 301 (47.55)   | 10 (1.56)        | 56 (58.33)    | 245 (44.79)        | 0.111   |
| AMI, n (%)                       | 263 (41.22)   | 5 (0.78)         | 62 (64.58)    | 201 (37.08)        | <0.001  |
| Diabetes, n (%)                  | 207 (32.19)   | 0 (0)            | 33 (34.38)    | 174 (31.81)        | 0.62    |
| CAD, n (%)                       | 610 (96.06)   | 8 (1.24)         | 95 (98.96)    | 515 (95.55)        | 0.154   |
| **CKD stages**                   |               |                  |               |                    | <0.001  |
| CKD G3a, n (%)                   | 397 (61.74)   | 0 (0)            | 43 (44.79)    | 354 (64.72)        |         |
| CKD G3b, n (%)                   | 177 (27.53)   | 0 (0)            | 28 (29.17)    | 149 (27.24)        |         |
| CKD G4, n (%)                    | 59 (9.18)     | 0 (0)            | 22 (22.92)    | 37 (6.76)          |         |
| CKD G5, n (%)                    | 10 (1.56)     | 0 (0)            | 3 (3.13)      | 7 (1.28)           |         |
| **Laboratory examination**       |               |                  |               |                    |         |
| LDL-C, mmol/L                    | 2.68±0.89     | 149 (23.17)      | 2.81±1.05     | 2.66±0.86          | 0.281   |
| HDL-C, mmol/L                    | 0.95±0.28     | 149 (23.17)      | 0.98±0.26     | 0.95±0.29          | 0.471   |
| Lpa, mg/dL                       | 34.53±37.56   | 78 (12.13)       | 31.69±32.30   | 35.02±38.41        | 0.402   |
| Scr, μmol/L                      | 145.39±70.94  | 0 (0)            | 157.42±63.14  | 143.28±72.07       | 0.05    |
| eGFR, mL/min/1.73 mm²            | 45.71±11.40   | 0 (0)            | 40.76±12.88   | 46.58±10.91        | <0.001  |
| Serum urea nitrogen, mg/dL       | 7.79±4.02     | 5 (0.78)         | 8.56±4.40     | 7.65±3.94          | 0.062   |
| Haemoglobin, g/L                 | 125.43±17.65  | 84 (13.06)       | 118.40±20.20  | 126.76±16.86       | <0.001  |
| HbA1c, %                         | 6.77±1.39     | 147 (22.86)      | 6.79±1.34     | 6.77±1.40          | 0.912   |
| **Medications**                  |               |                  |               |                    |         |
| ACEI/ARB, n (%)                  | 551 (85.69)   | 0 (0)            | 72 (75.00)    | 479 (87.57)        | <0.001  |
| β-blocker, n (%)                 | 504 (78.50)   | 1 (0.16)         | 60 (62.50)    | 444 (81.92)        | <0.001  |
| Statin, n (%)                    | 616 (95.80)   | 0 (0)            | 91 (94.79)    | 525 (95.98)        | 0.581   |
| Diuretics, n (%)                 | 240 (37.33)   | 0 (0)            | 51 (53.13)    | 189 (34.55)        | <0.001  |
| **Procedure**                    |               |                  |               |                    |         |
| PCI, n (%)                       | 386 (69.30)   | 86 (13.37)       | 61 (85.92)    | 325 (66.87)        | 0.001   |
| Emergency procedure              | 165 (25.66)   | 0 (0)            | 41 (42.71)    | 124 (22.67)        | <0.001  |
| Hydration volume, mL             | 1091.42±669.98| 22 (3.42)        | 1325.13±875.55| 1050.25±618.81     | 0.004   |
| Contrast volume, mL              | 136.10±64.72  | 1 (0.16)         | 145.36±60.08  | 134.47±65.42       | 0.108   |
| Mehran Score                     | 8.37±5.28     | 17 (2.64)        | 11.82±8.45    | 7.77±9.65          | <0.001  |
| Periprocedure IABP, n (%)        | 64 (9.95)     | 0 (0)            | 22 (22.92)    | 42 (7.68)          | <0.001  |

ACEI, ACE inhibitors; AMI, acute myocardial infarction; ARB, angiotensin-receptor blockers; CAD, coronary artery disease; CI-AKI, contrast-induced acute kidney injury; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimate glomerular filtration rate; HDL-C, high density lipoprotein-C; HR, heart rate; IABP, intra-aortic balloon pump; LDL-C, low density lipoprotein-C; Lpa, lipoprotein a; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; Scr, serum creatinine.
The incidence of CI-AKI was 14.93% (n=96). Compared with those without CI-AKI, patients complicated with CI-AKI following CAG tended to have older age, higher heart rate and lower weight, haemoglobin and eGFR. Patients with CI-AKI were also more likely to have hypotension, acute myocardial infarction (AMI) and intra-aortic balloon pump (IABP), and they were less likely to be prescribed ACE inhibitors (ACEI)/angiotensin-receptor blockers and β-blocker. No significant difference between groups was identified in contrast volume, heart function and baseline Scr.

CI-AKI and long-term outcomes

The median follow-up period was 7.3 (4.5; 8.4) years. During the follow-up period, patients who developed CI-AKI following the procedure demonstrated worse long-term outcomes (log-rank p<0.001) (online supplementary figure 1). After adjusting for age, gender, heart rate, systolic blood pressure, LVEF, eGFR, diabetes mellitus and anaemia, CI-AKI was independently associated with higher risk of long-term death (Hazard ratio: 2.13, 95% CI 1.41 to 3.23) (online supplementary table 1). The Hosmer-Lemeshow statistic of multivariable analysis did not suggest a lack of fit ($\chi^2=12.146$, p=0.145).

These selected predictors were used to form a CI-AKI risk estimation nomogram (figure 1). The nomogram was internally validated with the bootstrap validation method (1000 times). The nomogram performed well in estimating the risk of CI-AKI, with an unadjusted C statistic of 0.78 (95% CI, 0.73 to 0.83, figure 2) and a bootstrap-corrected C statistic of 0.76. In addition, the nomogram demonstrated better predictive value among patients with CKD while compared with Mehran Score (p=0.024, figure 2), and there was also a good calibration curve for the risk estimation (figure 3). By NRI, applying the nomogram significantly improved classification (0.38; 95% CI 0.20 to 0.55).

The results of univariable logistic analysis are detailed in table 2. Through multivariable logistic analysis and backward stepwise approach, age (OR: 2.85; 95% CI 1.73 to 4.69), weight (OR: 0.66; 95% CI 0.44 to 0.98), heart rate (OR: 1.51; 95% CI 1.14 to 2.02), hypotension (OR: 16.38; 95% CI 3.11 to 86.39), PCI (OR: 3.27; 95% CI 1.56 to 6.88) and β-blocker (OR: 0.36; 95% CI 0.20 to 0.64) were selected as predictors of CI-AKI (table 3). The Hosmer-Lemeshow statistic of multivariable analysis did not suggest a lack of fit ($\chi^2=12.146$, p=0.145).

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Risk of CI-AKI based on the nomogram scores
Based on the predicted incidence of CI-AKI in relation to different total nomogram scores, we further divided the patients into four score categories: 50≤scores<100 (risk=1.53%), 100≤scores<150 (risk=10.46%), 150≤scores<200 (risk=37.25%) and scores≥200 (risk=85.50%) (online supplementary figure 2). The actual incidence of CI-AKI by score categories is also exhibited in online supplementary figure 2, with significant trends across increasing score values for predicting CI-AKI (Cochran Armitage $\chi^2$, p<0.001).

The optimal cut-off value of the total nomogram scores to identify patients at risk was determined to be 129. The sensitivity and specificity when used in differentiating the presence from absence of CI-AKI were 81.2% and 62.3%, respectively.

DISCUSSION
The present study might be the first one to develop a nomogram for the prediction of CI-AKI in patients with CKD undergoing CAG/PCI. Our result indicated that age, weight, heart rate, hypotension, PCI and $\beta$-blocker were independent predictors for CI-AKI. A nomogram based on these predictors demonstrated a good predictive value, which was better than that of the classic Mehran Score, as well as stabilisation and good calibration.

The incidence of CI-AKI among our CKD cohort was 14.93%, which was relatively high but rational as previous observations indicated that certain populations subsets, especially patients with advanced CKD, are at high risk of CI-AKI. Kroneberger et al found that an eGFR <45 mL/min/1.73m$^2$ was correlated with a higher risk for CI-AKI compared with an eGFR in the range of 45–60 mL/min/1.73m$^2$. Among the 643 patients with CKD in our study, the mean eGFR was 45.71±11.40 mL/min/1.73m$^2$, which may further explain the high incidence of CI-AKI.

We also found that the occurrence of CI-AKI was associated with a worse long-term outcome in a follow-up period as long as 7.3 years, which further verified the importance of CI-AKI prevention. However, we also noticed that it is difficult to conclude definitively that CI-AKI is responsible for long-term death. In contrast to our observation, a study conducted by Werner Ribitsch et al, including consecutive patients undergoing elective PCI or percutaneous transluminal angiography/angioplasty of peripheral arteries, renal arteries or carotids, found no significant difference in survival between patients with CI-AKI (88.6%) and without CI-AKI (84.7%, p=0.48) during the 2 years follow-up period. Differences in the study population may explain the controversial report. Indeed, CI-AKI is a marker rather than a mediator of an increased risk of worse long-term outcomes. The relationship between CI-AKI and worse long-term outcome may be explained as follows: First, patients who developed CI-AKI following CAG/PCI tended to have their kidney function deteriorate after this acute event, and deterioration in kidney function has long been reported as a strong indicator for adverse outcomes. Second, in our cohort, patients with CI-AKI tended to be complicated with haemodynamic instability or comorbidity associated with prognosis. Third, the distant organ effects of AKI, especially the effect leading to cardiac dysfunction, may have a significant impact on prognosis. Potential mechanisms may be endothelial dysfunction, fluid overload, hypercoagulation and myocardial depression activity during ultrafiltration.

In the present prediction model, age was one of the strongest risk predictors for CI-AKI development, which was similar to the previous results. Ling Ji et al developed a new post-PCI CI-AKI risk score model that incorporated several factors (ie, age >75 years) in the preoperative risk estimation of CI-AKI. Underweight was also an independent risk factor for CI-AKI, which has been reported in a previous study. A study conducted by Liu et al that included 12 555 Asian patients suggested that underweight was independently associated with AKI (OR 1.23, 95% CI 1.04 to 1.44), but not with overweight or obesity. Heart rate, a reflection of haemodynamics,
was an independent predictor for CI-AKI, which has been reported in previous studies.  
Perioperative haemodynamic disorders may lead to ischaemia-reperfusion injury, which may have a potential contribution to postoperative AKI. Moreover, compared with those who underwent CAG only, patients undergoing PCI were at higher risk of CI-AKI, which has also been seen in a previous study. In particular, use of a β-blocker was found to be a protective factor for CI-AKI in our CKD cohort. A study that enrolled 120 patients undergoing CAG or ventriculography has suggested that patients receiving 5 mg nebivolol (a β-blocker) every 24 hours for 4 days were associated with a significant decrease in mean Scr levels compared with the baseline levels. Furthermore, both selective β1-adrenergic receptor antagonist and non-selective β1-adrenergic receptor antagonist prevent development of CI-AKI in mice. The underlying mechanism may be decreasing oxidative stress, attenuation of the tubular necrosis, proteinaceous casts and medullary congestion. However, the existing evidence is limited to animal experiments and observational studies. In the future, evidences from high-quality randomised controlled trials are needed to support the effectiveness of preventing CI-AKI by β-blockers.

The present nomogram did not include some common risk factors, such as anaemia, contrast volume, the severity of procedural renal impairment (CKD stages) and hydration volume, though some observations and meta-analyses have indicated that these patient-associated and procedure-associated factors are independent predictors for CI-AKI. Similar to our findings, haemoglobin has been found in previous studies to be associated with CI-AKI in univariable, but not in multivariable, analyses. Our results suggest that the effect of haemoglobin level on CI-AKI may be substantially influenced by confounding factors, especially in patients with renal dysfunction. As for contrast volume, several studies have challenged that the development of AKI following contrast exposure is significantly determined by the presence of comorbidities and haemodynamic instability rather than contrast media. Moreover, a recent systemic review conducted by Mehran et al adapted the concept of contrast-associated AKI instead of contrast-induced AKI. In our cohort, no significant difference was detected in contrast volume between patients with or without CI-AKI. In addition, in the present study, we identified AMI, hypotension, heart rate and the need for IABP as independent risk factors for CI-AKI. These findings indicated that haemodynamic instability rather than contrast media may be the main and primary cause for AKI. The risk of CI-AKI due to contrast agents may have long been overrated. The severity of procedural renal impairment (CKD stages) was not included as a predictor in our model; this is somewhat surprising. A similar observation has been reported by Naoki Okumura et al, who included 105 consecutive patients with CKD and did not report eGFR as an independent risk factor. Moreover, the limited number of events (96 CI-AKI) in our cohort may not be able to support many variables, since the recommended events per variable is 10–20. Therefore, other variables regarding the haemodynamics may be of priority. Hydration has been recommended as an effective strategy for CI-AKI prevention, though evidence from randomised control trials is sparse. In the AMACING (A Maastricht Contrast-Induced Nephropathy Guideline) Trial, Nijssen et al randomly assigned 660 patients undergoing contrast exposure to receive either periprocedural intravenous isotonic saline or no hydration. No significant difference in the incidence of CI-AKI between the hydration group and the no-hydration group was observed (2.7% vs 2.6%). In our cohort, patients who developed CI-AKI following the procedure tended to have more hydration volume. This finding may be due to the higher incidence of hypotension in the CI-AKI group. In addition, potential interaction may exist between ‘Hydration volume’ and ‘Hypotension’, ‘Hydration volume’ and ‘weight’. Meanwhile, adding ‘Hydration volume’ to our model did not significantly improve the discriminative power (C statistic: 0.785 vs 0.777, p=0.2608) but made our model more complicated. Therefore, ‘Hydration volume’ was not included in our final model.

Strengths and limitations
To our knowledge, few previous prediction models for CI-AKI have focused on patients with CKD, though CKD is regarded as one of the strongest independent risk factors for CI-AKI. Our nomogram may be more clinically applicable among patients with CKD for its higher discriminated power and fewer variables, which enable physicians to identify patients at risk and take action in time. Also, the risk threshold of 129 points indicating a risk of around 10% was similar to the risk threshold of the Mehran Score. Our study had some limitations. First, this study was based on data from a single centre. However, our cohort is one of the largest CI-AKI databases regarding patients with CKD. Second, the present nomogram was not externally validated, though there was a calibration with 1000 bootstrap samples to decrease the overfit bias. Finally, some patients were discharged within 72 hours after CAG/PCI, so creatinine levels were not measured on day 3 in these patients, which might underestimate the incidence of CI-AKI. However, it is known that most CI-AKI occurs in the first 24 hours.

Conclusions
The present nomogram which was constructed based on a relatively large cohort of patients with CKD undergoing CAG/PCI demonstrated a better discriminative power but included fewer variables than the classic Mehran Score. With six predictors, the nomogram may be a simple and reliable tool to identify patients with CKD at risk of CI-AKI, whereas further external validations are in need.

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Data availability statement Data relevant to this study are available upon reasonable request to the corresponding authors.

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