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ORIGINAL ARTICLE

Impact of contrast-induced acute kidney injury on long-term major adverse cardiovascular events and kidney function after percutaneous coronary intervention: insights from a territory-wide cohort study in Hong Kong

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ABSTRACT

Background. The impact of contrast-induced acute kidney injury (CI-AKI) on long-term major adverse cardiovascular events (MACE) remains controversial.

Method. This was a retrospective cohort study from 14 hospitals under the Hospital Authority of Hong Kong between 2004 and 2017. Severe CI-AKI was defined as an increase in serum creatinine of >50% from the baseline value, an absolute increase of >1 mg/dL (88 μmol/L) or requiring dialysis after percutaneous coronary intervention (PCI). Mild CI-AKI was defined as an increase in serum creatinine of >25% from the baseline value or an absolute increase of >0.5 mg/dL (44 μmol/L) after PCI but not fulfilling the criteria for severe CI-AKI. The primary endpoint was MACE, defined as a composite outcome of all-cause mortality, non-fatal myocardial infarction after hospital discharge, stroke or any unplanned coronary revascularization, in a time-to-first-event analysis up to 5 years after PCI. The secondary endpoints were individual components of MACE and cardiovascular mortality.

Results. A total of 34 576 patients were analysed. After adjustment for cardiovascular risk factors, procedural characteristics and medication use, the risk of MACE at 5 years was significantly higher with mild CI-AKI {hazard ratio [HR], 1.18 [95% confidence interval (CI) 1.12–1.26); $P < 0.001$} and severe CI-AKI [HR 1.92 (95% CI 1.78–2.07); $P < 0.001$]. Severe CI-AKI was associated with higher adjusted risks of each secondary end point and the risks monotonically accrued over time.

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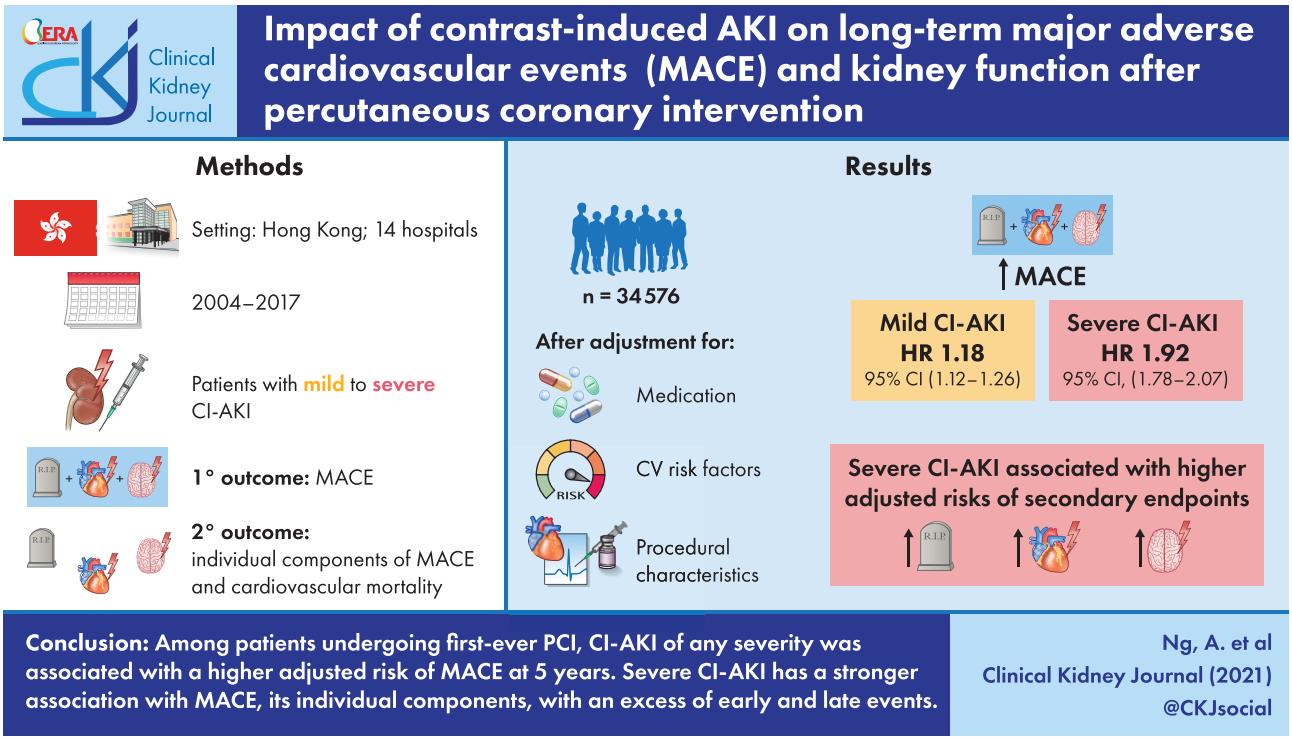
Conclusions. Among patients undergoing a first-ever PCI, CI-AKI of any severity was associated with a higher adjusted risk of MACE at 5 years. Severe CI-AKI has a stronger association with MACE and its individual components, with an excess of early and late events.

GRAPHICAL ABSTRACT



Keywords: all-cause mortality, cardiovascular mortality, chronic kidney disease, contrast induced acute kidney injury, major adverse cardiac events, myocardial infarction, percutaneous coronary intervention, repeat revascularization, stroke

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) occurs in 13–20% patients with coronary artery disease (CAD) undergoing percutaneous coronary interventions (PCIs) [1, 2]. Although CI-AKI is associated with worse renal outcomes [3–7], its relationship with long-term major adverse cardiovascular events (MACE) after PCI has been unclear. There is evidence showing that the association of CI-AKI and MACE is confounded by many factors and the risk of MACE attributable to CI-AKI was much attenuated after confounder adjustment [8]. In a pooled analysis of randomized trials, interventions that reduced CI-AKI did not result in an appreciable effect on long-term mortality or renal prognosis [9]. These results have cast doubts on the independent association between CI-AKI and MACE [10]. Furthermore, published data on late (>1 year) cardiovascular outcomes with regard to CI-AKI remain relatively limited.

Prevention of CI-AKI has been advocated as a means to improve outcomes after PCI, contingent upon its relationship with MACE. For example, a lower incidence of CI-AKI was considered an important mechanism, as radial access can lead to better clinical outcomes [11, 12]. In other scenarios, CI-AKI was presumed to be the limiting factor in delivering better outcomes in more complex procedures, such as multivessel PCI for patients with cardiogenic shock [13]. It is, therefore, important to evaluate the relationship between CI-AKI and long-term cardiovascular outcomes. Our present study aimed to determine the patterns of association between CI-AKI after PCI and long-term MACE in a territory-wide registry-based study.

MATERIALS AND METHODS

Study population and design

Data from all patients who underwent first-ever PCI between 1 January 2004 and 31 December 2017 from all 14 public hospitals that performed PCI and recorded in a territory-wide PCI registry were reviewed. Patients' baseline characteristics, exposures and outcomes were retrieved from the PCI Registry and Clinical Data and Analysis Reporting System. The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority.

We included all adult patients (≥18 years of age) who underwent first-ever PCI and survived for at least 7 days after PCI. Exclusion criteria were patients who were dialysis dependent, had unknown baseline estimated glomerular filtration rate (eGFR) or eGFR < 10 mL/min/m^2 or had no serum creatinine level measured within 7 days after PCI.

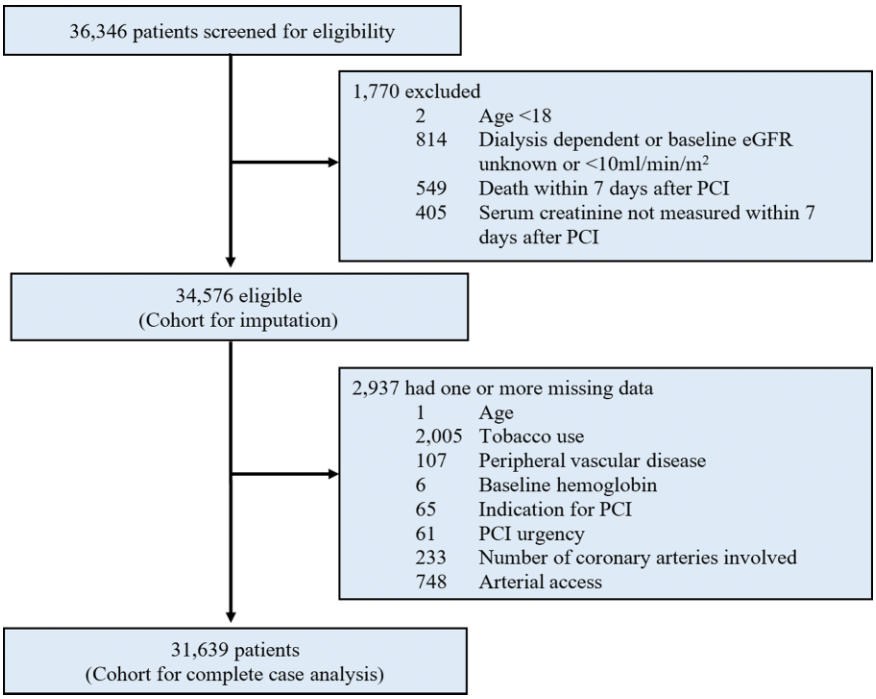


FIGURE 1: Study profile.

Definitions of exposure and outcome variables

Severe CI-AKI was defined as an increase in serum creatinine of >50% from the baseline value, an absolute increase of >1 mg/dL (88 μmol/L) [14, 15] or requiring dialysis within 7 days after PCI. Mild CI-AKI was defined as an increase in serum creatinine of >25% from baseline value, an absolute increase of >0.5 mg/dL (44 μmol/L) within 7 days after PCI but not fulfilling criteria for severe CI-AKI [16, 17]. The primary endpoint was MACE, defined as a composite outcome of all-cause mortality, non-fatal myocardial infarction (MI) after hospital discharge, stroke or any unplanned coronary revascularization, as a time-to-first-event analysis up to 5 years after PCI. The secondary endpoints were individual components of MACE and cardiovascular mortality. The detailed definitions are shown in the Supplementary Appendix.

Statistical analysis

All analyses were performed with prespecified endpoints and statistical methods. Unadjusted analyses were made using the chi-squared test for categorical variables and the Kruskal–Wallis test or one-way analysis of variance for continuous variables. Cox regression analysis was performed to evaluate the independent relationship between CI-AKI and clinical outcomes, adjusting for potential confounders selected *a priori* based on published data and biological plausibility. Variables adjusted were gender [14], age, tobacco use, diabetes mellitus [18], hypertension, dyslipidaemia, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, previous MI, previous coronary artery bypass surgery, history of heart failure, atrial fibrillation, anti-coagulant use, renin–angiotensin blocker use [19], history of cancer, cirrhosis, eGFR [18, 20], baseline anaemia (haemoglobin <13 g/dL for men and <12 g/dL for women) [21], haemoglobin decrease of >2 g/dL after PCI [21], urgency of PCI [20], indication for PCI [20], number of arteries affected, intravascular imaging use, radial access use, decompensated heart failure [22], cardiogenic shock [20, 22], mechanical circulatory support [22] and time period of PCI performed.

Sensitivity analyses

The analysis was repeated to assess the relationship between CI-AKI defined and staged by the Kidney Disease: Improving Global Outcomes (KDIGO) and the outcomes of interest [12].

To assess for any residual confounding by treatment selection, we performed falsification testing with a new diagnosis of cancer after PCI. It was selected based on its association with MACE but was biologically unlikely to be causally related to CI-AKI [23, 24].

The complete case method was adopted to address missing data in the primary statistical analysis. To test the robustness of our results, the regression analysis was repeated with the entire cohort using the technique of multiple imputations by chained equations.

Exploratory analyses

We explored the time-varying effects of CI-AKI on MACE. Outcomes were examined separately between 0 and 1 month, 1 and 12 months, 12 and 36 months and 36 and 60 months using the same regression model in the primary analysis.

We further divided patients with CI-AKI according to any loss of kidney function at 90 days after PCI. Loss of kidney function (i.e. irreversible CI-AKI) was defined as an increase in serum creatinine of >25% from the baseline value or an absolute increase of >0.5 mg/dL (44 μmol/L). The risks of MACE occurring between 90 days and 5 years were compared among patients without

Table 1. Baseline characteristics of patients

Characteristics	No CI-AKI	Mild CI-AKI	Severe CI-AKI	P-value[a]
Patients, *n*	25 998	4091	1550	
Female gender	5888 (22.6)	1210 (29.6)	583 (37.6)	<0.001
Age (years), mean (SD)	64.3 (11.3)	65.5 (11.9)	69.1 (11.6)	<0.001
Tobacco use	12 285 (47.3)	1814 (44.3)	606 (39.1)	<0.001
Diabetes mellitus	8883 (34.2)	1527 (37.3)	720 (46.5)	<0.001
Hypertension	16 376 (63.0)	2599 (63.5)	1132 (73.0)	<0.001
Dyslipidaemia	16 723 (64.3)	2301 (56.2)	865 (55.8)	<0.001
Cerebrovascular disease	2270 (8.7)	415 (10.1)	235 (15.2)	<0.001
Peripheral artery disease	302 (1.2)	65 (1.6)	64 (4.1)	<0.001
Chronic obstructive pulmonary disease	669 (2.6)	115 (2.8)	49 (3.2)	0.28
Previous cancer	1219 (4.7)	209 (5.1)	103 (6.6)	0.002
Cirrhosis	51 (0.2)	7 (0.2)	7 (0.5)	0.085
Previous MI	3324 (12.8)	448 (11.0)	214 (13.8)	0.002
Previous CABG	385 (1.5)	67 (1.6)	45 (2.9)	<0.001
History of heart failure	1811 (7.0)	398 (9.7)	285 (18.4)	<0.001
eGFR, mean (SD)	80.3 (21.1)	86.3 (25.6)	68.2 (33.2)	<0.001
eGFR <60 mL/min/m^2	4312 (16.6)	711 (17.4)	655 (42.3)	<0.001
Baseline anaemia[b]	6958 (26.8)	1494 (36.5)	903 (58.3)	<0.001
Atrial fibrillation	1204 (4.6)	237 (5.8)	140 (9.0)	<0.001
Chronic anticoagulation at baseline	553 (2.1)	119 (2.9)	57 (3.7)	<0.001
Angiotensin blockade at baseline	13 249 (51.0)	1944 (47.5)	768 (49.5)	<0.001

Values presented as *n* (%) unless stated otherwise. SD, standard deviation; CABG, coronary artery bypass surgery.
[a]P-value indicates any difference between the three groups.
[b]Anaemia: haemoglobin <13 g/dL for men and <12 g/dL for women.

CI-AKI, with reversible CI-AKI and with irreversible CI-AKI. Events earlier than 90 days after PCI were excluded to avoid reverse causality.

A risk score was developed to predict the occurrence of severe CI-AKI. All patients were randomly divided in a 1:1 ratio into development and validation cohorts. Backward step-wise logistic regression analysis was used to identify the strongest risk factors of severe CI-AKI with a probability value of threshold 5% and was used in the selection model building process. The area under the receiver operating characteristics curve (AUC-ROC) was used to evaluate the model discrimination between patients with and without severe CI-AKI.

Data management and statistical analyses were performed using Stata, version 16 (StataCorp LP, College Station, TX, USA). For the primary endpoint, a two-tailed P-value <0.05 was considered statistically significant. For the secondary endpoints, Bonferroni correction was used to adjust for multiplicity and therefore a two-tailed P-valve <0.01 was considered statistically significant.

RESULTS

Patients and characteristics

Between January 2004 and December 2017, a total of 36 346 patients were considered for inclusion: 1770 (4.9%) were excluded for any of the following exclusion criteria: age <18 years, on regular renal replacement therapy or baseline eGFR <10 mL/min/m^2, death within 7 days after PCI or serum creatinine not measured within 7 days after PCI. Of the remaining 34 576 patients analysed, a total of 2937 (8.5%) were excluded from the complete case analysis due to missing values in any of the variables used in the Cox regression model (Figure 1). Mild CI-AKI developed in 4091 (12.9%) patients and severe CI-AKI developed in 1550 (4.9%) patients, including 242 (0.8%) requiring dialysis. Table 1 shows the baseline characteristics of the study population. Table 2 shows the procedural characteristics and medications on discharge of the study population.

Primary outcome

The primary outcome of MACE occurred in 7187 (27.6%) patients in the no CI-AKI group, 1402 (34.3%) in the mild CI-AKI group and 938 (60.5%) patients with severe CI-AKI during the observation period (Table 3 and Figure 2). In adjusted analysis, the risk of MACE at 5 years was significantly higher with mild CI-AKI {hazard ratio [HR] 1.18 [95% confidence interval (CI) 1.12–1.26]; P < 0.001} and severe CI-AKI [HR 1.92 (95% CI 1.78–2.07); P < 0.001] (Table 4).

Secondary outcomes

Severe CI-AKI was associated with higher risks of all of the individual secondary outcomes. Mild CI-AKI was associated with higher risks of all-cause mortality, cardiovascular mortality, myocardial infarction and unplanned revascularization, but not stroke (Tables 3 and 4).

Sensitivity analyses

CI-AKI according to the KDIGO definition occurred in 3642 (11.5%) patients, including 3001 (9.5%) with stage 1, 219 (0.7%) with stage 2 and 444 (1.4%) with stage 3 AKI. In adjusted analysis, the risk of MACE at 5 years was significantly higher with CI-AKI [HR 1.46 (95% CI 1.38–1.54); P < 0.001]. The risk was also higher with each increment in the stage of CI-AKI [HR 1.36 (95% CI 1.32–1.41); P < 0.001]. The secondary outcomes of all-cause mortality, cardiovascular mortality, MI, stroke and unplanned revascularization were all significantly higher with CI-AKI and each increment in the stage of CI-AKI (Supplementary data, Table S1).

Table 2. Procedural characteristics and medications at hospital discharge of patients

Characteristics	No CI-AKI	Mild CI-AKI	Severe CI-AKI	P-value
Patient, *n*	25 998	4091	1550	
Urgency of PCI				
Elective	17 292 (66.5)	1881 (46.0)	532 (34.3)	<0.001
Urgent	6393 (24.6)	1317 (32.2)	489 (31.5)	
Emergent	2313 (8.9)	893 (21.8)	529 (34.1)	
Indication for PCI				
Stable CAD	5389 (20.7)	590 (14.4)	141 (9.1)	<0.001
Unstable angina	5724 (22.0)	650 (15.9)	189 (12.2)	
NSTEMI	12 400 (47.7)	1950 (47.7)	741 (47.8)	
STEMI	2485 (9.6)	901 (22.0)	479 (30.9)	
NYHA class III–IV	820 (3.2)	249 (6.1)	239 (15.4)	<0.001
Cardiogenic shock	369 (1.4)	138 (3.4)	165 (10.6)	<0.001
Ventricular tachycardia	473 (1.8)	186 (4.5)	144 (9.3)	<0.001
Number of epicardial artery affected				
One vessel	11 890 (45.7)	1671 (40.8)	484 (31.2)	<0.001
Two vessels	8675 (33.4)	1388 (33.9)	549 (35.4)	
Three vessels	5433 (20.9)	1032 (25.2)	517 (33.4)	
Left main artery disease	1439 (10.2)	284 (11.7)	182 (17.1)	<0.001
Mechanical circulatory support	215 (0.8)	105 (2.6)	123 (7.9)	<0.001
Intravascular imaging	10 747 (41.3)	1774 (43.4)	615 (39.7)	0.016
Intravascular ultrasonography	8198 (31.5)	1364 (33.3)	507 (32.7)	0.052
Optic coherence tomography	2661 (10.2)	433 (10.6)	113 (7.3)	<0.001
Contrast volume (mL), median (IQR)	140 (100–190)	150 (105–200)	150 (100–200)	<0.001
Angiographical success	25 322 (97.5)	3971 (97.1)	1458 (94.1)	<0.001
Haemoglobin decrease >2 g/dL after PCI	4465 (17.2)	660 (16.1)	588 (37.9)	<0.001
Aspirin on discharge	25 225 (97.0)	3986 (97.4)	1514 (97.7)	0.14
P2Y12 inhibitor on discharge	25 696 (98.8)	4060 (99.2)	1517 (97.9)	<0.001
Angiotensin blockade on discharge	17 250 (66.4)	3022 (73.9)	1169 (75.4)	<0.001
Beta blocker on discharge	19 059 (73.3)	3044 (74.4)	1200 (77.4)	<0.001
Statin on discharge	23 525 (90.5)	3661 (89.5)	1350 (87.1)	<0.001
Year of PCI				
2004–2008	5671 (21.8)	863 (21.1)	338 (21.8)	0.017
2009–2012	7394 (28.4)	1246 (30.5)	395 (25.5)	
2013–2016	6706 (25.8)	1021 (25.0)	421 (27.2)	
2016–2017	6227 (24.0)	961 (23.5)	396 (25.5)	

Values presented as *n* (%) unless stated otherwise. NSTEMI, non-ST elevation MI; STEMI, ST elevation MI; NYHA, New York Heart Association; IQR, interquartile range.

Table 3. Unadjusted annualized risks (95% CI) of primary and secondary outcomes

Outcomes	No CI-AKI	Mild CI-AKI	Severe CI-AKI
Primary			
MACE	7.32% (7.16–7.50)	9.78% (9.28–10.31)	25.42% (23.84–27.10)
Secondary			
All-cause mortality	2.17% (2.09–2.26)	3.30% (3.04–3.58)	13.50% (12.50–14.56)
Cardiovascular mortality	0.73% (0.69–0.78)	1.30% (1.14–1.48)	6.19% (5.53–6.92)
MI	3.07% (2.96–3.17)	4.24% (3.93–4.58)	9.12% (8.25–10.09)
Stroke	1.35% (1.29–1.42)	1.70% (1.51–1.90)	3.49% (3.00–4.08)
Unplanned revascularization	2.43% (2.33–2.52)	2.99% (2.73–3.27)	5.08% (4.45–5.80)

Falsification testing showed that the risk of cancer diagnosed after PCI was not associated with mild CI-AKI [HR 1.07 (95% CI, 0.89–1.28); P = 0.49] or severe CI-AKI [HR 0.96 (95% CI 0.72–1.27); P = 0.77].

A total of eight variables in the Cox regression model had missing data. Tobacco use, the variable that had the largest amount of missing data, had 2005 (5.8%) missing values. Multiple imputation was conducted and the imputed cohort included all 2937 (8.5%) patients who were excluded due to missing values in any of the variables used in the model. In the imputed dataset, the risks of MACE were significantly higher with mild CI-AKI [HR 1.20 (95% CI 1.13–1.27); P < 0.001] and severe CI-AKI [HR 1.94 (95% CI 1.81–2.09); P < 0.001], both consistent with the complete case cohort.

Exploratory analyses

The excess risk of MACE associated with mild CI-AKI was highest in the first month but became insignificant for events occurring after 12 months (Table 5). The excess risk of MACE associated

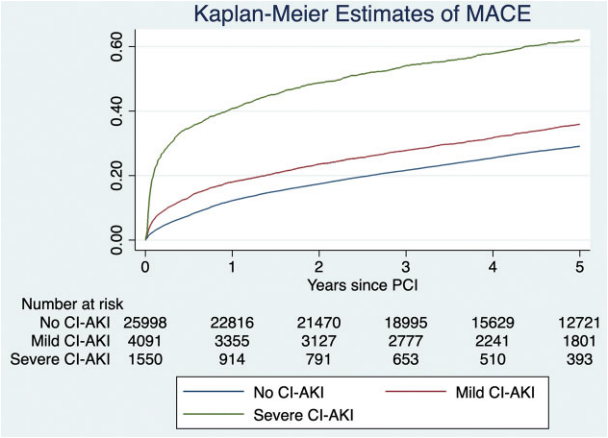


FIGURE 2: Unadjusted estimated probabilities of MACE stratified by CI-AKI severity. Kaplan–Meier curves showing more severe CI-AKI was associated with a higher risk of MACE in unadjusted analysis.

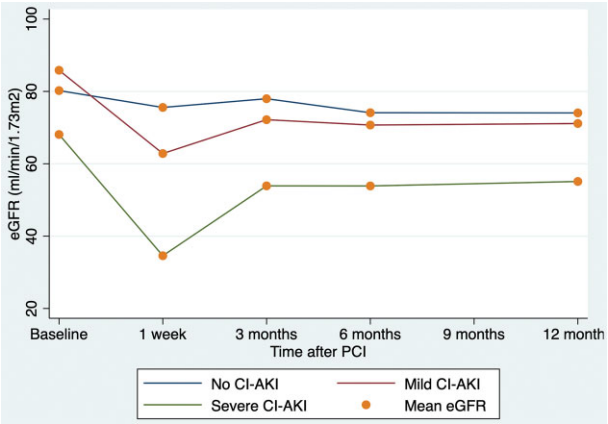


FIGURE 3: Trajectory of eGFR. Change in mean eGFR by CI-AKI.

with severe CI-AKI was highest in the first month but remained significant throughout various landmarks during the observation period.

The risks of sustained loss of kidney function throughout the first year were increased with a greater severity of CI-AKI (Figure 3 and Supplementary data, Table S2). Loss of kidney function at 90 days after PCI developed in 558 (2.6%) patients without AKI, 144 (3.2%) patients with mild CI-AKI and 537 (30.2%) patients with severe AKI (P for trend <0.001). The adjusted risks of MACE were higher in both patients with reversible CI-AKI [HR 1.19 (95% CI 1.11–1.28); P < 0.001] and irreversible CI-AKI [HR 1.18 (95% CI 1.09–1.29); P < 0.001], compared with patients without CI-AKI. However, the adjusted risks of MACE were not significantly different among those with irreversible CI-AKI and reversible CI-AKI [HR 0.99 (95% CI 0.89–1.10); P = 0.89].

Seven variables (Supplementary data, Table S3) were included in the logistic regression equation. The final risk score was developed with a range of −1 to 12 and could be calculated as follows: baseline anaemia (2 points), baseline eGFR <30 mL/min/m^2 (3 points), history of heart failure (1 point), urgent or emergent PCI (2 points), unstable haemodynamics (any cardiogenic shock, need for mechanical circulatory support, decompensated heart failure or ventricular tachyarrhythmia) (2 points), radial access (–1 point) and haemoglobin decrease >2 g/dL (2 points). The AUC-ROC (C-statistic) was 0.82 (Figure 4). The optimal cut-off for prediction of severe CI-AKI was ≥3 points, conferring a sensitivity of 72% and specificity of 76%. The risk score model correlated well in the validation group (risk of severe CI-AKI 5.6%, sensitivity 72%, specificity 76% and C-statistic 0.80).

DISCUSSION

Our data from this territory-wide PCI registry demonstrated that CI-AKI was associated with a higher adjusted risk of MACE at 5 years in patients undergoing first-ever PCI and such an association was further enhanced in those with severe CI-AKI. In this cohort, the annualized risk of MACE was almost 10% in those with mild CI-AKI and up to 25% in those with severe CI-AKI, relatively lower than results from prior studies with shorter follow-up periods [25, 26]. In patients with severe CI-AKI, the risk of MACE was increased by almost 2-fold and we also observed that severe CI-AKI was associated with higher adjusted risks of all-cause mortality, cardiovascular mortality, MI, stroke and coronary revascularization individually, along with a higher risk of subsequent loss of kidney function. The excess risks of MACE monotonically accrued for severe CI-AKI but not for mild CI-AKI.

CI-AKI is a well-recognized risk factor for worse patient survival and renal outcomes regardless of the baseline renal function [3–7]. Nonetheless, the relationship of CI-AKI with cardiovascular outcomes remains controversial. Our present

Table 4. Adjusted HR of primary and secondary outcomes

	Mild CI-AKI		Severe CI-AKI	
Outcomes	HR (95% CI)	P-value	HR (95% CI)	P-value
Primary				
MACE	1.18 (1.12–1.26)	<0.001	1.92 (1.78–2.07)	<0.001
Secondary				
All-cause mortality	1.27 (1.16–1.40)	<0.001	2.85 (1.59–3.14)	<0.001
Cardiovascular mortality	1.43 (1.23–1.67)	<0.001	3.21 (2.77–3.73)	<0.001
MI	1.21 (1.11–1.32)	<0.001	1.64 (1.46–1.84)	<0.001
Stroke	1.12 (0.98–1.28)	0.087	1.45 (1.22–1.73)	<0.001
Unplanned revascularization	1.15 (1.04–1.27)	0.008	1.56 (1.34–1.80)	<0.001

Adjusted variables were gender, age, tobacco use, diabetes mellitus, hypertension, dyslipidaemia, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, previous MI, previous coronary artery bypass surgery, history of heart failure, atrial fibrillation, anticoagulation use, renin–angiotensin blocker use, history of cancer, cirrhosis, eGFR, baseline, haemoglobin decrease >2 g/dL after PCI, urgency of PCI, indication for PCI, number of arteries affected, intravascular imaging use, radial access use, decompensated heart failure, cardiogenic shock, mechanical circulatory support and time period of PCI performed.

Table 5. Adjusted HR of MACE at various landmarks

	Mild CI-AKI		Severe CI-AKI	
MACE	HR (95% CI)	P-value	HR (95% CI)	P-value
0–1 month	1.82 (1.57–2.13)	<0.001	3.58 (3.05–4.21)	<0.001
1–12 months	1.13 (1.02–1.24)	0.019	1.67 (1.47–1.89)	<0.001
12–36 months	1.07 (0.96–1.20)	0.21	1.64 (1.41–1.91)	<0.001
36–60 months	1.13 (1.00–1.30)	0.06	1.39 (1.13–1.72)	0.002

Adjusted variables were gender, age, tobacco use, diabetes mellitus, hypertension, dyslipidaemia, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, previous MI, previous coronary artery bypass surgery, history of heart failure, atrial fibrillation, anticoagulation use, renin–angiotensin blocker use, history of cancer, cirrhosis, eGFR, baseline, haemoglobin decrease >2 g/dL after PCI, urgency of PCI, indication for PCI, number of arteries affected, intravascular imaging use, radial access use, decompensated heart failure, cardiogenic shock, mechanical circulatory support and time period of PCI performed.
CI-AKI, contrast induced acute kidney injury.

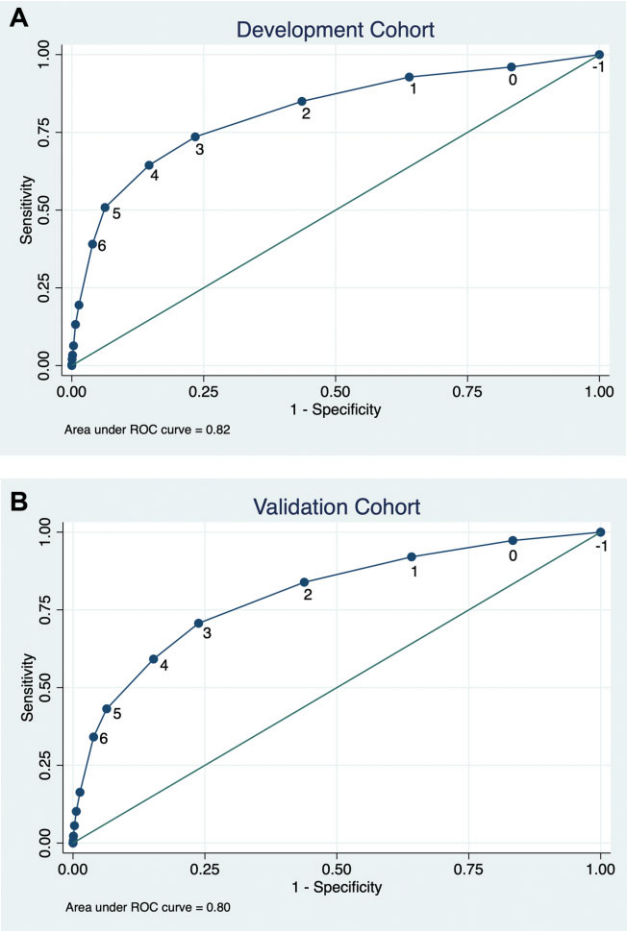


FIGURE 4: ROC of the risk score. ROC of the risk score, ranging from –1 to 12, in prediction of severe CI-AKI in (**A**) the development cohort and (**B**) the validation cohort. The optimal cut-off was ≥3 points.

observations were in line with several meta-analyses that demonstrated an unadjusted elevated risk of MACE in patients who developed CI-AKI. A large meta-analysis of 139 603 patients by James *et al.* [8] found a much attenuated yet significant association between CI-AKI and MACE after adjustment for confounders. Another meta-analysis of 32 781 patients by Yang *et al.* [27] showed a 1.5- to 2-fold increase in the risk of MACE for patients who developed CI-AKI after PCI, although there was no adjustment for potential confounders. In a pooled analysis of 9512 patients from two randomized trials, CI-AKI was found to be independently associated with a 1.5-fold increase in 1-year MACE in patients with acute coronary syndrome [26]. Data from 853 patients in a recent registry showed no association between CI-AKI and MACE, although the follow-up period was modest (16 months) and events were infrequent [5]. Kurogi *et al.* [28] examined 952 patients who had undergone primary PCI and concluded that persistent renal dysfunction after CI-AKI was independently associated with long-term mortality and stroke but not MI. While the effect of CI-AKI on long-term cardiovascular outcomes remains much debated, the insufficient awareness of contrast volume reduction in patients at risk of CI-AKI is still an important concern [29].

In the current study, both mild and severe CI-AKI were strong independent predictors of MACE and the association was severity dependent. The excess risks were highest within the first month after PCI and decreased with time. Nonetheless, these differences persisted for 5 years after PCI, with a pattern of monotonic accruement for severe CI-AKI but not mild CI-AKI. Both reversible and irreversible CI-AKI were related to worse cardiovascular outcomes. These findings suggest that CI-AKI has an important short-term and long-term impact on cardiovascular outcomes. Indeed, previous studies have demonstrated that AKI is associated with heightened risks of chronic kidney disease, and end-stage kidney disease even among patients who recovered completely from AKI [30–32]. Coupled with the insensitivity of serum creatinine level to detect a small decrease in eGFR, subclinical CKD could exist even in patients with apparent renal recovery [33]. There is strong evidence indicating patients with CKD of various severity have a strikingly worse cardiovascular prognosis after PCI [34–36]. Moreover, the severity of CI-AKI was highly predictive of subsequent loss of renal function, thus implying a pathophysiological link between the severity of CI-AKI and long-term MACE. Another putative mechanism is cytokine release from CI-AKI that directly causes inflammation, apoptosis and fibrosis at the cellular level, resulting in markedly reduced coronary vascular tone, reserve and vessel reactivity [10, 37, 38]. Such a cardiorenal relationship is increasingly recognized and our observations are in concordance with such postulation.

While there is emerging interest to leverage the prevention of CI-AKI to improve the long-term prognosis after PCI, it is important to identify at-risk patients who may benefit from these preventive strategies. The discriminative power of the previous prediction model for CI-AKI was only modest [22, 39]. In this context, we developed and internally validated a risk prediction model using simple clinical parameters to predict the occurrence of severe CI-AKI. It has excellent discriminative power (C-statistic ≥0.8) and can provide timely risk stratification to help clinicians take preventive measures in high-risk groups. Potential measures to prevent CI-AKI include adequate hydration, radial access and reduction of contrast administration by using intravascular ultrasound. Indeed, our current data support that the radial approach might be protective for CI-AKI. Previous meta-analysis from nine clinical trials also suggested that radial access was associated with a reduction in CI-AKI [40]. In a substudy from the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox randomized trial, CI-AKI was implicated as an important mechanistic explanation for better clinical outcomes in patients using the radial access approach [11]. Other strategies to

minimize contrast exposure include the application of intravascular ultrasound, as demonstrated in the Minimizing cOntrast utiliZation With IVUS Guidance in coRonary angioplasTy and Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock randomized trials, although various limitations have affected the generalizability of these studies. In this context, our currently developed prediction model may help select at-risk patients to further verify and harness the beneficial effects of intravascular ultrasound to reduce CI-AKI in PCI.

Limitations of this study include its observational nature and the exclusion of patients who were dialysis dependent or with eGFR <10 mL/min. Also, even though every patient had at least one renal function result after PCI, the test was not mandated to be repeated and this may lead to potential under identification of CI-AKI. The inclusion of only patients who had a first-ever PCI may have been biased to a lower risk of CI-AKI, as those with prior PCI, in particular those undergoing a staged procedure, may have fewer untreated lesions requiring PCI [26]. Nevertheless, our data were retrieved from a population-based electronic database with minimal loss to follow-up and complete information on laboratory results and subsequent events, thus representing relatively comprehensive and real-world data. Other merits of our study include its large sample size from a territory-wide registry, extensive adjustment of potential confounders (e.g. baseline medical history, clinical presentation, procedural complexity, medication use and complications) and *a priori* capture of clinical data, which minimizes the selection, information and recall biases.

CONCLUSION

CI-AKI was associated with a higher adjusted risk of MACE at 5 years in patients undergoing a first-ever PCI and such risk was severity dependent. Prevention of CI-AKI represents as an important strategy to optimize cardiovascular outcomes for patients undergoing PCI.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

AUTHORS' CONTRIBUTORS

A.K.N., D.Y.Y. and C.W.S. were responsible for the conception and design of the study. A.K.N. analysed the data collected by A.I., L.L., I.W.L. and A.S.W. A.K.N. interpreted the data. A.K.N. and P.Y.N. drafted the manuscript. All authors revised and approved the final manuscript and are accountable for the accuracy and integrity of the work.

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CONFLICT OF INTEREST STATEMENT

The authors report no potential conflicts of interest.

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