Heart, Lung and Circulation (2019) **28,** 866–873
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.04.291

ORIGINAL ARTICLE

Clinical Implications of Contrast-Induced Nephropathy in Patients Without Baseline Renal Dysfunction Undergoing Coronary Angiography

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Received 28 September 2017; received in revised form 14 April 2018; accepted 22 April 2018; online published-ahead-of-print 16 May 2018

Background The clinical implications of different definitions of contrast-induced nephropathy (CIN) in patients without baseline renal dysfunction are not well defined.

Methods Consecutive patients at a single centre without baseline renal dysfunction (estimated glomerular filtration rate, eGFR $\geq$ 60 ml/min/1.73 m^2) undergoing coronary angiography or percutaneous coronary intervention (PCI), were systematically evaluated for long-term risk of mortality following CIN using two broad definitions: an absolute increase from baseline in serum creatinine (SCr) $\geq$0.3 mg/dl (mild to severe absolute CIN) and a relative increase from baseline of 25% (mild to severe relative CIN) within 72 hours.

Result Of 2,823 subjects alive before discharge following coronary angiography there were 320 episodes of mild to severe relative CIN (11.3%) and 125 of mild to severe absolute CIN (4.4%). During a median follow-up of 2.3 years, 73 patients (3.2%) died. After adjustment for confounders, mild to severe absolute CIN was associated with an adjusted hazard ratio (HR) (95% confidence interval) for all-cause mortality of 3.31 (1.74-6.30) ($p < 0.0001$) and relative CIN with an adjusted HR of 1.92 (1.09, 3.38) ($p = 0.024$). The risk of mortality rose with severity of CIN. Two commonly used definitions of CIN combining absolute and relative terms (increase $\geq$ 0.3 mg/dl or 50%, and $\geq$ 0.5 mg/dl or 25% from the baseline) confirmed these results.

Conclusion Among patients without baseline renal dysfunction undergoing coronary angiography, the incidence of CIN can range widely depending on definition. Absolute CIN is less common than relative CIN. Regardless of definition, CIN is associated with a markedly increased risk of long-term mortality. This finding requires confirmation in multicentre studies.

Keywords Contrast-induced nephropathy • Renal dysfunction • Coronary angiography • Mortality

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Introduction

Contrast-induced nephropathy (CIN) is a common complication after coronary angiography with or without percutaneous coronary intervention (PCI). In high risk patients, such as those with baseline renal dysfunction (estimated glomerular filtration rate, eGFR <60 ml/min/1.73 m^2), the incidence can be as high as 20% [1]. Previous studies have suggested an association between CIN and adverse cardiovascular events, renal events and mortality [2,3]. The magnitude of this increased risk in patients without baseline renal impairment is not well understood. Furthermore, multiple definitions of CIN are in use, which complicates between-study comparisons and understanding of the likely impact of preventative measures. Using a CIN definition of ≥0.5 mg/dl or ≥25% rise in serum creatinine (SCr), Dangas et al. reported worse in-hospital and 1-year outcomes in patients undergoing coronary angiography which extended also to patients without baseline renal dysfunction [4]. Conversely, Abe et al. found no association between CIN (defined as a ≥0.5 mg/dl rise in SCr) and long-term mortality in patients without baseline renal dysfunction. In a sensitivity analysis they confirmed this finding using the alternate definition of a ≥0.3 mg/dl or ≥25% rise in SCr [1]. Therefore, the true clinical implications of CIN in patients without baseline renal dysfunction and the impact of various absolute or relative increases in SCr used in the definition remain controversial.

In the present study, we used a prospective study database of patients undergoing coronary angiography to investigate the incidence of CIN using different absolute and relative increases in SCr to define a variety of CIN definitions. We then assessed the long-term mortality risk associated with these different definitions.

Methods

Subjects

This prospective observational cohort of patients undergoing coronary angiography at Guangdong General Hospital, China was recruited between January 2010 and December 2013 [5,6]. Those with at least one SCr measurement before and one within 24–72 hours after the index angiography and who were discharged alive were included. Exclusion criteria included age <18 years, pregnancy, lactation, intravascular administration of a contrast medium within the previous 7 days or 3 days post operation, no use of low-osmolarity contrast agents, cardiovascular surgery or endovascular repair, end-stage renal disease or renal replacement, missing preoperative or postoperative SCr, malignancy, and no use of isotonic saline for hydration. We also excluded patients who died during the index hospitalisation or presented with baseline eGFR <60 ml/min/1.73 m^2. (Supplementary Figure 1).

The Guangdong General Hospital Ethics Research Committee approved the study, and all patients gave their written informed consent prior to undergoing angiography. Follow-up events were monitored and recorded by trained nurses or medical research assistants through office visits or telephone interviews at 1, 6, 12, 24, 36 and 48 months after coronary angiography.

Coronary Angiography or Intervention and Hydration

Coronary angiography was performed according to standard clinical practice, according to AHA/ACCF guidelines [7]. All patients received nonionic, low-osmolality contrast agents. Patients received a continuous intravenous infusion of isotonic saline at a rate of 1 ml/kg/h (0.5 ml/kg/h in cases of left ventricular ejection fraction [LVEF] <40% or severe congestive heart failure) for at least 2–12 hours before and 6–24 hours after the procedure [5,6]. We calculated the eGFR using the Modification of Diet in Renal Disease (MDRD) formula [8].

Definitions

Baseline renal dysfunction was defined as eGFR < 60 ml/min/1.73 m^2 [1,4] prior to coronary angiography. Contrast-induced nephropathy was defined in two ways. Absolute CIN was defined by a rise in SCr from baseline ≥0.3 mg/dl at 48–72 hours after coronary angiography. It was categorised as mild, moderate or severe (an increase of 0.3-0.49 mg/dl, 0.5–0.99 mg/dl or ≥1.0 mg/dl respectively). Relative CIN was defined by a ≥25% increase in SCr from baseline at 48–72 hours and was similarly subcategorised as mild, moderate or severe (25–49%, 50–99% and ≥100% respectively). We classified it according to the staging system for acute kidney injury "RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria" [17]. We also adopted two frequently used composite definitions of CIN, the first (CIN-1) defined as an increase in SCr ≥0.3 mg/dl or 50% from baseline within 48 hours after coronary angiography, and the second (CIN-2) defined asan increase in SCr ≥ 0.5 or 25% within 48–72 hours after coronary angiography from baseline [10,11].

Major adverse clinical events were recorded, including all-cause mortality, non-fatal myocardial infarction (MI), target vessel revascularisation, CIN requiring renal replacement therapy, stroke, and all-cause re-hospitalisation.

Statistical Analysis

Continuous variables are expressed as the mean ± SD and were compared using the Student t test or Wilcoxon rank-sum test according to their distributions. Categorical variables are presented with numbers and percentages and were compared using the chi-square test or Fisher's exact test. Univariate and multivariable logistic regression be used to investigate the predictors of CIN based on baseline characteristics pre-angiography. The cumulative incidence of all-cause death was estimated by the Kaplan-Meier method, and differences were assessed with the log-rank test. The adjusted relationships between CIN and death after discharge were evaluated using Cox proportional hazard models. Candidate predictors that were significant at $p < 0.05$ in univariate analysis and were clinical important were included in the

Cox regression models [9]. The results of analysis are shown as the hazard ratio (HR) given with 95% confidence intervals (CIs) and p-values.

Scatter plot analyses were performed to observe the predictive value of absolute CIN and relative CIN for long-term mortality after adjustment for confounders. Potential confounders were either known predictors of long-term mortality or baseline parameters that were seen to differ significantly in frequency between groups when the cohort was stratified by a) mortality or b) moderate absolute CIN [11]. A two-sided p-value <0.05 was considered significant for all analyses. All data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Clinical Characteristics and Frequency of CIN

Of 4,153 patients with both pre- and post-procedure SCr measurements, 2,823 met the inclusion criteria and were included in the study (Supplementary Figure 1). The study population was predominantly male (77.6%) with a mean age of 61 ± 11years and the majority of procedures (79.8%) were non-emergent. The clinical characteristics of patients are presented in Table 1. Baseline characteristics were significantly different between patients with and without moderate-severe absolute CIN (Table 1). Absolute CIN of any severity occurred in 125 patients (4.4%) with 13 (0.5%) having severe, 28 (1.0%) moderate and 84 (3.0%) mild CIN. Relative CIN was more common, occurring in 320 patients (11.3%). Of these, 17 (0.6%) were severe, 45 (1.6%) moderate and 258 (9.1%) mild degree. Of the commonly used definitions of CIN, CIN-2 (321 patients, 11.4%) occurred more often than CIN-1 (115 patients, 4.1%). Baseline characteristics between patients with CIN-1 and patients with CIN-2 are shown in Supplementary Table 1 (CIN-1 vs CIN-2, 115 patients compared to 321 patients).

Pre-Procedural Predictors of CIN

Multivariate logistic regression analysis revealed that age ≥75 (odds ratio [OR], 2.13; 95% confidence interval [CI], 1.05-4.80), congestive heart failure (4.42, 95% CI, 2.15-9.07) were pre-procedurally independent predictor of CIN.

In-Hospital and Long-Term Clinical Outcome

The mean follow-up period was 2.3 ± 0.8 years (median 2.2; interquartile range, 1.7–2.9 years). Seventy-three (73) (3.2%) patients died during follow-up. Patients with moderate-severe absolute CIN had a higher incidence of in-hospital and follow-up adverse outcomes, including mortality, heart failure and re-hospitalisation (Table 2). The unadjusted all-cause mortality of patients with any definition of CIN was significantly higher than that of patients without CIN (Figures 1 and 2) (Table 2). Moreover, the different definitions of CIN were each associated with different long-term mortality risks (Table 3).

Predictive Value of CINs for Long-Term Mortality

In the Cox proportional hazards model, after adjustment for age, weight, diabetes, anaemia, congestive heart failure, heart rate, use of diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta blockers or calcium channel blockers, patients with any degree of absolute CIN (increase ≥ 0.3 mg/dl) or any degree of relative CIN (increase ≥ 25%) were significantly more likely to suffer long-term mortality (adjusted HR 6.10 (3.4–11.0, $p < 0.0001$) and 3.0 (1.7–5.0, $p < 0.001$), respectively). More severe degrees of CIN (relative or absolute) were associated with greater increase in risk of mortality (Table 3). Similar results were obtained using either of the two common definitions of CIN (CIN-1 or CIN-2) (Table 3 and Figure 3).

Discussion

This prospective study extends previous observational studies of CIN in patients undergoing coronary angiography to the more general cohort of patients without baseline renal dysfunction and highlights the wide variation in incidence and prognosis of CIN depending on the definition used. Overall, CIN as defined by a relative rise in SCr was more common than CIN defined by an absolute rise. Regardless of definition, CIN is clearly associated with long-term mortality in patients undergoing coronary angiography, even in those without baseline renal dysfunction.

No universally accepted consensus definition of CIN exists. Different definitions may result in quite different estimates of the incidence and clinical significance of CIN. The typical definition consists of an absolute increase in SCr from baseline following the administration of contrast of ≥ 0.5 mg/dl, a relative increase of ≥ 25%, or combination of both (either ≥ 0.5 mg/dl or ≥ 25%) [10–14]. Society guidelines and trials include widely differing criteria based on distinct sources such as RIFLE (≥50% within 7 days), Acute Kidney Injury Network (AKIN) (≥0.3 mg/dl or ≥50% or reduced urine output) or Kidney Disease Improving Global Outcomes (KDIGO) (≥50% or ≥0.3 mg/dl) [15,16]. Other definitions, such as >0.4 mg/dl, >1.0 mg/dl or >100%, have also been used [17–19]. Any consensus definition must define an entity with well-understood clinical significance. A large collaborative registry (n = 58,957) found that a definition of CIN based on an absolute rise in SCr of ≥0.5 mg/dl in patients undergoing PCI resulted in a higher incidence (6.4% vs 3.2%) than a definition based on a relative increase of ≥25% and was superior at identifying patients at greater risk for adverse renal and cardiac events [17]. The results of the present study of patients without baseline renal dysfunction are similar, although it is important to note that CIN defined by a relative increase in SCr was still significantly correlated with long-term mortality.

Table 1 Baseline characteristics between patients with and without common moderate to severe absolute moderate to severe absolute contrast induced nephropathy (≥0.5 mg/dl).

Variable	Entire cohort without baseline renal dysfunction (n = 2,823)	Contrast induced nephropathy (≥0.5 mg/dl)		P-value
		Yes (n = 41)	No (n = 2,782)	
Demographic variables				
Age, years	61.35 ± 10.86	66.12 ± 11.63	61.28 ± 10.83	0.005
Age >75 years	280 (9.92)	10 (24.39)	270 (9.71)	0.004
Men	2190 (77.58)	33 (80.49)	2157 (77.53)	0.653
Weight, kg	65.18 ± 10.77	62.20 ± 9.91	65.23 ± 10.77	0.073
Smokers	1151 (40.77)	18 (43.90)	1133 (40.73)	0.681
Hypertension	1488 (52.71)	23 (56.10)	1465 (52.66)	0.662
Diabetes mellitus	609 (21.57)	4 (9.76)	605 (21.75)	0.064
Anaemia	782 (27.70)	13 (31.71)	769 (27.64)	0.564
Hyperlipidaemia	425 (15.05)	4 (9.76)	421 (15.13)	0.339
Congestive heart failure	346 (12.26)	21 (51.22)	325 (11.68)	<0.001
Previous MI	256 (9.07)	4 (9.76)	252 (9.06)	>0.999
Previous CABG	22 (0.78)	NA (NA)	22 (0.79)	>0.999
Examination				
HR (mean ± sd)	74.74 ± 12.86	78.95 ± 18.22	74.68 ± 12.76	0.142
SBP, mmHg	128.74 ± 19.53	125.12 ± 22.67	128.80 ± 19.48	0.232
DBP, mmHg	76.36 ± 11.66	73.78 ± 9.77	76.39 ± 11.68	0.154
Hypotension	59 (2.09)	7 (17.07)	52 (1.87)	<0.001
LVEF	58.80 ± 11.72	47.41 ± 15.81	58.97 ± 11.57	<0.001
LVEF <40%	195 (7.96)	10 (27.78)	185 (7.66)	<0.001
Baseline Scr, μmol/L	80.24 ± 16.14	85.53 ± 18.37	80.16 ± 16.09	0.034
eGFR, ml/min/1.73m^2	79.05 ± 24.69	67.57 ± 23.30	79.22 ± 24.68	0.003
Baseline CrCl, mL/min	89.44 ± 20.76	83.13 ± 22.78	89.53 ± 20.72	0.050
HbA1c, %	6.48 ± 1.30	6.47 ± 1.12	6.48 ± 1.30	0.965
HDL-C, mmol/L	1.01 ± 1.43	1.01 ± 0.30	1.01 ± 1.43	0.994
LDL-C, mmol/L	3.75 ± 41.86	2.86 ± 0.83	3.76 ± 42.13	0.907
Medication Therapy				
Diuretic	413 (14.63)	19 (46.34)	394 (14.16)	<0.001
ACEI/ARB	2480 (87.85)	33 (80.49)	2447 (87.96)	0.225
β-Blockers	2431 (86.11)	29 (70.73)	2402 (86.34)	0.004
Calcium channel blockers	454 (16.08)	5 (12.20)	449 (16.14)	0.495
Procedure characteristics				
Emergency PCI	571 (20.23)	18 (43.90)	553 (19.88)	<0.001
Coronary lesions	1.89 ± 1.11	2.27 ± 1.14	1.88 ± 1.11	0.027
No. of stent used	1.38 ± 1.21	1.41 ± 1.02	1.38 ± 1.22	0.856
Total stent length, mm	32.50 ± 32.47	35.02 ± 32.76	32.47 ± 32.47	0.617
Contrast volume, mL	124.40 ± 64.30	128.41 ± 66.36	124.35 ± 64.28	0.688

Values are reported as mean ± standard deviation or n (%).

Abbreviations: Baseline renal dysfunction： Evaluated glomerular filtration rate <60 ml/min/1.72 m^2; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; Scr: serum creatinine; eGFR, evaluated glomerular filtration rate; CrCl: creatinine clearance; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blocker; PCI, percutaneous coronary intervention.

The Cardiovascular Research Foundation (CRF) angioplasty database suggested that CIN was one of the most powerful predictors of 1-year mortality in patients with pre-existing baseline renal dysfunction or preserved eGFR after adjustment of confounders [4]. The CRF database was restricted to patients undergoing first PCI and excluded patients with acute ST-elevation myocardial infarction. Our study confirms the prognostic importance of CINs for long-term mortality among patients without baseline renal dysfunction and extends these findings to the general cohort undergoing coronary angiography with the benefit of longer follow-up duration (mean 2.3 vs 1 year). Therefore CRF

Table 2 **In-hospital and long-term outcomes for patients with or without CIN (moderate to severe absolute CIN (increase ≥0.5 mg/dL).**

	All patients	CIN (increase ≥0.5 mg/dl)	Non-CIN (increase ≥0.5 mg/dl)	P-value
In-hospital outcomes				
AHF	40 (1.42)	9 (21.95)	31 (1.11)	<0.001
RRT	10 (0.35)	6 (14.63)	4 (0.14)	<0.001
New-AMI	5 (0.18)	NA (NA)	5 (0.18)	>0.999
Arrhythmia	75 (2.66)	5 (12.20)	70 (2.52)	0.001
Stroke	6 (0.21)	2 (4.88)	4 (0.14)	0.003
Bleeding	13 (0.46)	2 (5.13)	11 (0.40)	0.013
Long-term outcomes				
Mortality	73 (3.20)	8 (27.59)	65 (2.89)	<0.001
RRT	3 (0.13)	1 (4.17)	2 (0.09)	0.009
Stroke	15 (0.68)	NA (NA)	15 (0.69)	>0.999
TVR	7 (2.64)	2 (28.57)	5 (1.94)	0.012
Re-hospitalisation	358 (18.22)	6 (33.33)	352 (18.08)	0.173

Abbreviations: CIN, contrast-induced nephropathy; AHF, acute heart failure; RRT, renal replacement therapy; AMI, acute myocardial infarction; TVR, target vessel revascularisation.

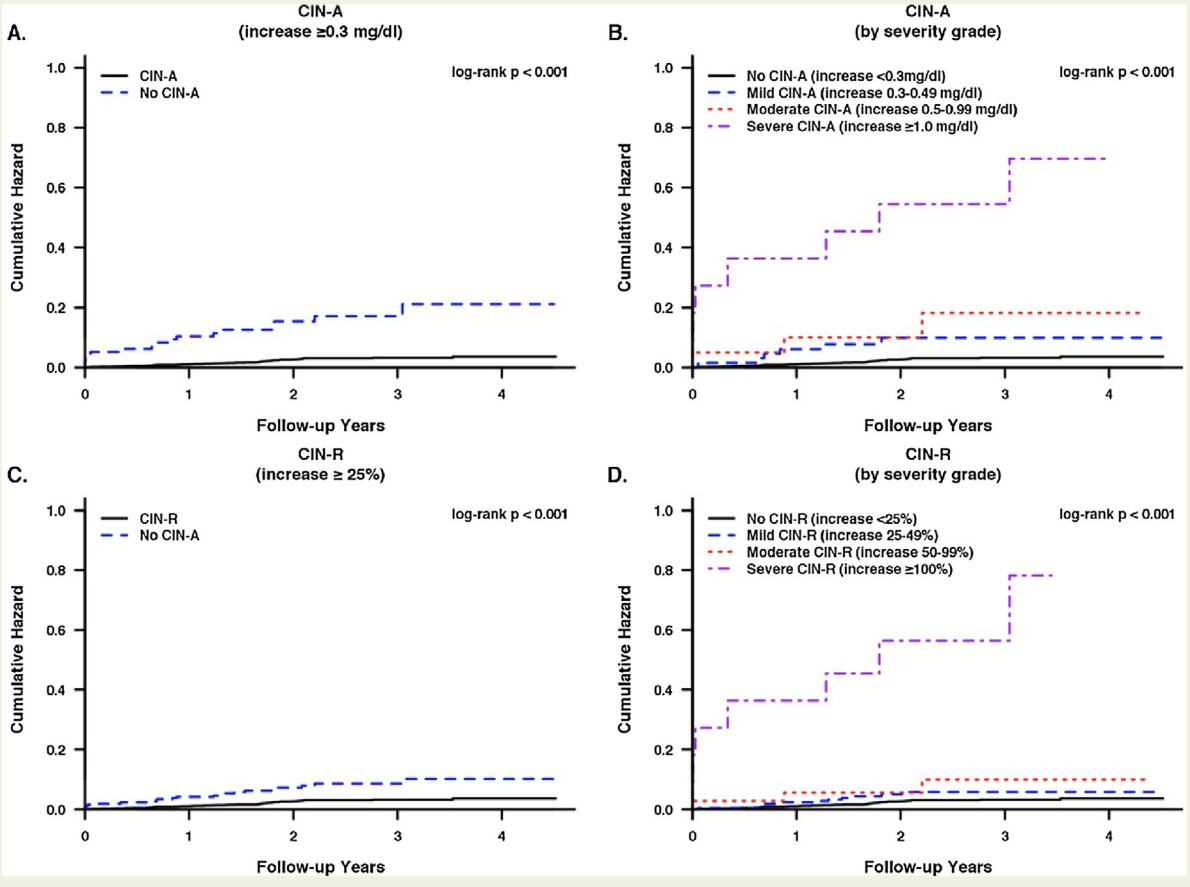

Figure 1 Severity of CIN and mortality.
Legend: Both absolute and relative CIN of any severity (A and C) are associated with increased mortality. The mortality risk varies greatly with severity of CIN (B and D). Absolute CIN (CIN-A), Relative CIN (CIN-R).
Abbreviations: CIN, contrast-induced nephropathy.

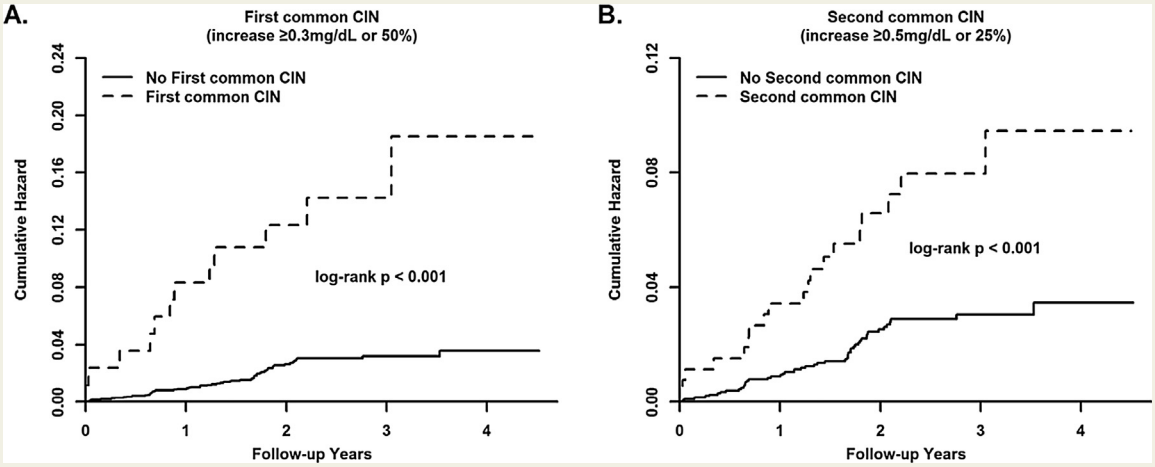

Figure 2 Common CINs and mortality.
Abbreviations: CIN, contrast-induced nephropathy.

database study's definition of CIN, the baseline risk, and the follow-up period were different from our study, we also confirmed our results by sensitivity analyses using various definitions of CIN, as previously mentioned.

A recent retrospective study, Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto), found CIN to be significantly correlated with long-term mortality in patients with baseline renal dysfunction but not in those without baseline renal dysfunction [5]. The CREDO-Kyoto cohort had higher mortality (8.6% vs 3.2%) with longer follow-up duration (3.5 vs 2.3 year) than the present study, although similar confounders were included in the adjusted prognostic model (12 vs 11). A previous study showed that the rate of moderate to severe absolute CIN (≥0.5 mg/dL) was 6.4% in patients with acute coronary syndrome (at higher risk of CIN) and normal renal function, which was mildly higher than ours (4%) [20]. Their findings may have suffered from ascertainment bias as a relatively high number of patients lacked a post-procedure SCr measurement.

Contrast-induced nephropathy identifies patients with a greater burden of comorbidity and that the association with increased mortality and long-term adverse outcome in patients who develop CIN reflects that burden. Contrast induced-AKI is not always a transient, but rather a direct cause of worsening renal function with increased risk of cardiovascular or all-cause death [21,22].

In the present study, relative CIN was more common than absolute CIN. It follows that defining CIN by a ≥ 25% rise in SCr may be more sensitive for detecting high-risk patients among those without baseline renal dysfunction. However, clinical context and co-morbidity may modify the relationship between CIN and mortality. Ultimately, an individualised approach to defining what is, or is not, clinically significant CIN that includes factors such as baseline renal

Table 3 Univariate and Multivariate Cox analysis for CINs (absolute, relative and common definitions) to predict long-term all-cause mortality following coronary angiography.

CINs	n, (%)	Univariate analysis			Multivariate Cox analysis		
		HR	95% CI	P-value	HR[a]	95%CI	P-value
Mild to severe absolute CIN (≥0.3 mg/dl)	125 (4.4%)	6.10	(3.40, 10.98)	<0.001	3.31	(1.74, 6.30)	<0.001
Moderate to severe absolute CIN (≥0.5 mg/dl)	41 (1.5%)	10.59	(5.07, 22.15)	<0.001	4.56	(2.00, 10.38)	<0.001
Severe absolute CIN (≥1.0 mg/dl)	13 (0.5%)	27.40	(11.85, 63.34)	<0.001	12.95	(5.00, 33.55)	<0.001
Mild to severe relative CIN (≥25%)	320 (11.3%)	2.95	(1.74, 5.00)	<0.001	1.92	(1.09, 3.38)	0.024
Moderate to severe relative CIN (≥50%)	62(2.2%)	6.48	(3.10, 13.54)	<0.001	3.43	(1.54, 7.64)	0.003
Severe relative CIN (≥100%)	17 (0.6%)	30.31	(13.11, 70.09)	<0.001	10.27	(4.03, 26.21)	<0.001
1st common CIN (≥0.3 mg/dl or ≥50%)	115 (4.1%)	5.57	(2.99, 10.39)	<0.001	3.04	(1.54, 6.00)	0.001
2nd common CIN (≥0.5 mg/dl or ≥25%)	321 (11.4%)	2.95	(1.74, 5.00)	<0.001	1.92	(1.09, 3.38)	0.024

Abbreviations: CIN, contrast-induced nephropathy; HR: hazard ratio; CI: confidence interval.
[a]adjusted confounders including age, weight, diabetes, anaemia, congestive heart failure, myocardial infarction history, ejection fraction, diuretic medication, angiotensin-converting enzyme inhibitors or angiotensin receptor blocker, beta blocker.

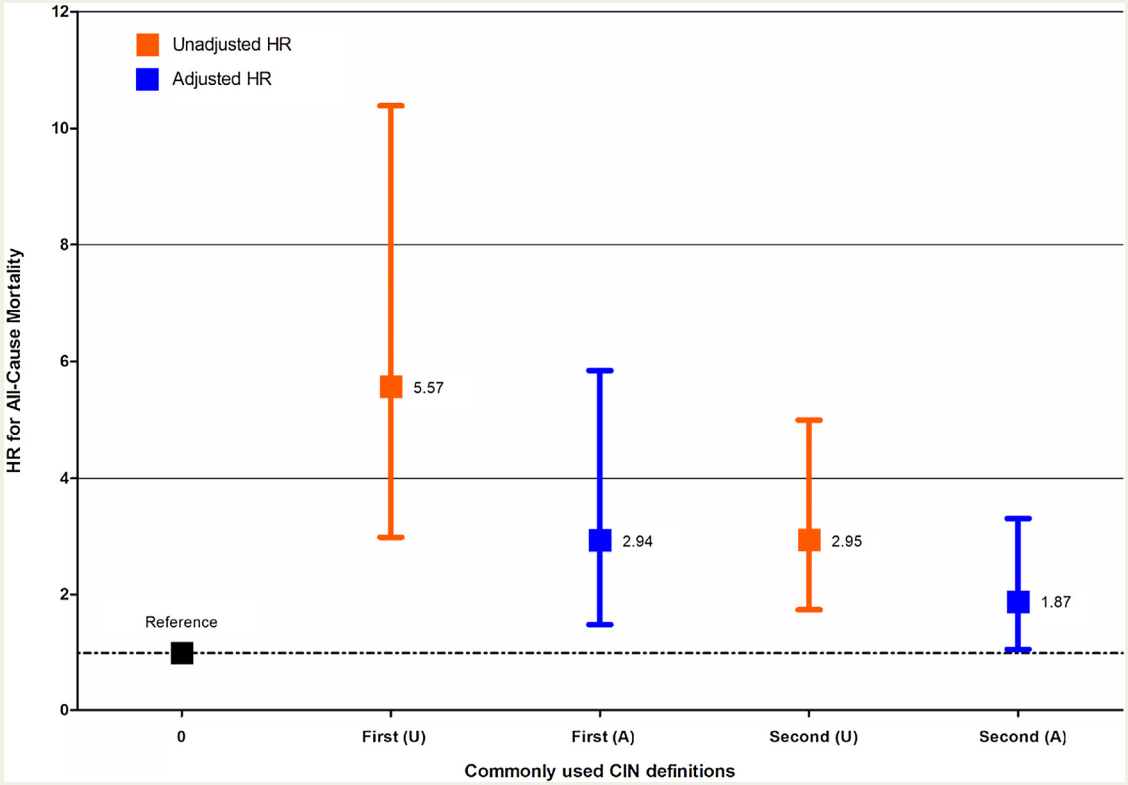

Figure 3 Unadjusted and adjusted HR for Common CINs.
First common CIN, an increase in SCr $\geq$ 0.3 mg/dl or 50% from baseline within 48 h; Second common CIN, an increase in SCr $\geq$ 0.5 or 25% with 48–72 h; U, unadjusted; A, adjusted.
Abbreviations: CIN, contrast-induced nephropathy; SCr, serum creatinine.

function, patient age and the presence of co-morbidities such as heart failure or diabetes is required. This would permit more nuanced assessment and application of preventative measures such as hydration with saline. Further information from large multicentre studies is required to inform this discussion.

Limitation

This study has several limitations. First, this is a single centre study with relatively small sample size. Second, we calculated the eGFR using the modification of diet in renal disease (MDRD) formula, rather than a direct measurement. Third, variations in measurement time may have resulted in not capturing post-procedure peak SCr levels. This variation and lack of measurement data may have led to an underestimation of the true development of CIN in this study population. Fourth, long-term mortality, which served as the primary endpoint, was low, and high risk patients such as the elderly were under-represented. A high rate of loss to follow-up (22% at 1 year) may have affected our ascertainment of long-term mortality and resulted in the low observed mortality rate. Finally, a uniform protocol for intravenous hydration was not strictly applied in this observational study which may limit the generalisability of the results.

Conclusions

Our data in an unselected population undergoing coronary angiography showed that, among patients without baseline renal dysfunction, absolute CIN might be less common than relative CIN. However, CIN of any degree or definition was significantly associated with long-term mortality. This finding supports the use of a relative definition (increase $\geq$ 25%) for risk stratification post-procedure. However, further large multicentre trials will allow a better understanding of the long-term impact of CIN in a wider variety of patients.

Acknowledgement

The authors thank the efforts of statistician, An Fan, MD, Guangdong, China.

Funding

This work was supported by the Guangdong Provincial Cardiovascular Clinical Medicine Research Fund (grant number 2009X41); Science and Technology Planning Project of Guangdong Province study by Y.L. in 2011 and study

grant number 2008A030201002); and the Guangdong Cardiovascular Institute.

Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2018.04.291.

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