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Could late measurement of serum creatinine be missed for patients without early increase in serum creatinine following coronary angiography?

Yong Liu, MD[a], Chong-yang Duan, MS[b,c], Kun Wang, MD[a], Wei-jie Bei, MD[a], Xiao-sheng Guo, MD[a], Hua-long Li, MD[a], Ying Wang, MD, PhD, FRACP[d], Shi-qun Chen, MS[a,e], Ying Xian, MD[f], Ping-yan Chen, MS[b,c,*], Qing-shan Geng, MD[a,*], Ning Tan, MD, FACC, FESC[a,*], Ji-yan Chen, MD, FACC, FESC[a,*]

Abstract

Most patients are discharged early (within 24 hours) after coronary angiography (CAG) and may miss identification the late (24–48 hours) increase in serum creatinine (SCr), whose characteristics and prognosis have been less intensively investigated.

We prospectively recruited 3065 consecutive patients with SCr measurement, including only1344 patients with twice SCr measurement (both early and late). The late contrast-induced acute kidney injury (CI-AKI) was defined as significantly increase in SCr (≥0.3 mg/dL or ≥50%) not in early phase, but only in late phase after the procedure, and the early CI-AKI experienced a significantly increase in early phase.

Overall, CI-AKI developed in 134 patients (10%), and the incidence of late and early CI-AKI were 3.6% and 6.4%, respectively. There were no difference in age, renal, and heart function, contrast volume among patients with late and early CI-AKI. With mean follow-up period of 2.45 years, long-term mortality (3 years, 29.7% and 35.6%, respectively, $P = .553$) was similar for patients with late and early CI-AKI. Cox analysis showed that both late (adjusted HR 2.05; 95% CI, 1.02–4.15) and early (adjusted HR 2.68; 95% CI, 1.57–4.59) CI-AKI was significantly associated with long-term mortality (all $P < .001$).

Only late increase in SCr, as late CI-AKI, accounted for about one-third of CI-AKI incidence and has similar good predictive value for long-term mortality with that of an early increase, early CI-AKI, among patients with SCr measured twice, supporting the importance of late repeating SCr measurement after CAG, even without an early significant increase in SCr.

Abbreviations: CAG = coronary angiography, CI-AKI = contrast-induced acute kidney injury, CrCl = creatinine clearance, MACE = major adverse clinical events, PCI = percutaneous coronary intervention, SCr = serum creatinine.

Keywords: contrast-induced acute kidney injury, coronary angiography, mortality, percutaneous coronary intervention

1. Introduction

Contrast-induced acute kidney injury (CI-AKI) is a serious complication after coronary angiography (CAG) or percutaneous coronary intervention (PCI), which is associated with prolonged hospitalization and increased health-care costs, morbidity, and mortality.[1–3]

CI-AKI is usually defined as an increase in the serum creatinine (SCr) level from baseline 48 to 72 hours after contrast exposure.[4–7] However, with the development of new technology, most patients are discharged within 24 hours after CAG or PCI, without late (24–48 hours) measurement of SCr. Recently, an early postprocedural increase of SCr ≥0.5 mg/dL (SCr values were available in 92.8% of patients at 24 hours and in an

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[a] Department of Cardiology, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, [b] State Key Laboratory of Organ Failure Research, National Clinical Research Center for Kidney Disease, [c] Department of Biostatistics, School of Public Health, Southern Medical University, Guangzhou, China, [d] Renal and Metabolic Division, The George Institute for Global Health, The University of Sydney, Camperdown, Australia, [e] Department of Biostatistics, Guangdong General Hospital Zhuhai Hospital, Zhuhai Golden Bay Center Hospital, Guangdong, China, [f] Duke Clinical Research Institute, Durham, NC, USA.

[*] Correspondence: Ji-yan Chen, Ning Tan, Qing-shan Geng, Department of Cardiology, Guangdong provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, School of Medicine, South China University of Technology, Guangzhou 510100, China (e-mails: chenjiyandr@126.com, tanning100@126.com, gengqsh@vip.tom.com); Ping-yan Chen, State Key Laboratory of Organ Failure Research, National Clinical Research Center for Kidney Disease, Guangzhou 510515, China (e-mail: chenpy99@126.com).

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additional 6.8% from 24 and 48 hours in the large observational study) was adopted to define CI-AKI, whose findings were cited for the calculation of maximum volume of contrast media to prevent CI-AKI by clinical guidelines, though its predictive value for long-term outcomes was not described and investigated.[8,9] Therefore, the risk of CI-AKI may be underestimated by absence of systematic 48- and 72-hour sampling due to the frequency of early discharge (within 24 hours) in real-world clinical practice,[10] though early (within 24 hours) abnormal increase of SCr has not been accepted by the tradition definition of CI-AKI (48–72 hours) used in most studies and prevention trials. The distribution of patients who develop CI-AKI in the early versus late phases is unknown, and in particular, there is lack of knowledge regarding the incidence and predictive value of a late (24–48 hours postprocedure) SCr increase for patients who do not show an early (within the first 24 hours) increase after CAG or PCI.

In the present study, we investigated the distribution of patients who developed CI-AKI in the early and late phases, and determined the predictive value of early and late phase CI-AKI for long-term mortality. In particular, we sought to determine the clinical significance of a late occurrence of CI-AKI, defined as significantly increase in SCr (SCr $\geq$0.3 mg/dL or $\geq$50%) that occurs not in early phase (within 24 hours), but only in the late phase (24–48 hours) after the procedure.

2. Methods

2.1. Subjects

In this prospective observational study, we reviewed all consecutive patients who underwent CAG or PCI between January 2010 and October 2012 at Guangdong General Hospital. As previously described,[11] we included patients aged $\geq$18 years who agreed to remain at the hospital to undergo monitoring for 2 to 3 days after CAG or PCI. We excluded patients according to the updated European Society of Urogenital Radiology Contrast Media Safety Committee guidelines.[12] The exclusion criteria included pregnancy, lactation, intravascular administration of a contrast medium within the previous 7 or 3 days postoperation (n = 83), no use of low-osmolarity contrast agents (n = 130), cardiovascular surgery or endovascular repair (n = 382), end-stage renal disease or renal replacement (n = 7), missing preoperative or postoperative creatinine (n = 61), malignancy (n = 3), no use of isotonic saline for hydration (n = 18), and missing day 2 SCr measurement (n = 208). After these exclusions, our analysis included 1721 patients with early single SCr measurement and 1344 patients with SCr measured twice after CAG or PCI.

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The first author drafted the manuscript, and all the authors made the decision, with approval from the steering committee, to submit the manuscript for publication.

2.2. Coronary angiography

CAG was performed according to standard clinical practice, using standard guide catheters, guidewires, balloon catheters, and stents via a femoral or radial approach. The contrast medium dose was chosen at the discretion of the interventional cardiologist. All patients received nonionic, low-osmolarity contrast agents (either iopamiron or iopromide, both 370 mg I/mL). Subjects were treated according to AHA/ACCF guidelines.[9] According to the local institutional protocol,[13] SCr concentrations were measured at hospital admission and on days 1 and 2 after CAG.

The creatinine clearance (CrCl) rate was calculated by applying the Cockcroft–Gault formula to the SCr concentration,[14] and the contrast media volume to CrCl (V:CrCl) ratio was calculated. We previously promoted hydration (IV fluids) protocol for the patients, who 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 <40% or severe congestive heart failure) for at least 2 to 12 hours before and 6 to 24 hours after the procedure.

2.3. Primary endpoint and definitions

The primary endpoint of this study was CI-AKI, defined as an increase in SCr $\geq$0.3 mg/dL or $\geq$50% within 48 hours after the procedure, and compared to baseline. Early CI-AKI was defined as an increase in SCr within the early phase (<24 hours), with or without increase in the late phase (24–48 hours) after the procedure. Late CI-AKI was defined as an increase in SCr that occurred only in the late phase after the procedure. Major adverse clinical events (MACE) were defined as a composite of all-cause mortality, nonfatal myocardial infarction, target vessel revascularization, CI-AKI requiring renal replacement therapy, stroke, and all-cause rehospitalization. Follow-up events were monitored and recorded by trained nurses through office visits or telephone interviews at 1, 6, 12, 24, 36, and 48 months after CAG or PCI. The mean follow-up period was 2.51 $\pm$ 0.86 years (median, 2.45; interquartile range, 1.80–3.27 years).

2.4. Statistical analysis

We grouped 3065 consecutive patients into 1721 patients with early single SCr measurement after CAG and another 1344 patients with both early and late repeat SCr measurements among whom we divided the CI-AKI patients into those with early or late CI-AKI. The clinical and biochemical characteristics and in-hospital clinical outcomes of each group, created on the basis of whether CI-AKI occurred or not, are presented as frequencies and percentages for categorical variables and as the mean $\pm$ standard deviation for continuous variables. Comparisons between normally distributed continuous variables were performed using *t* tests. The Pearson chi-squared or Fisher exact test were used, as appropriate, for categorical data analysis.

Univariate and multivariate analyses were performed using the log-rank test and Cox regression analyses to assess whether patients who developed late CI-AKI were at increased risk of long-term death. The data were analyzed on an available case basis, and missing data were not imputed. For multivariable models, cases missing values of included factors were excluded listwise. Candidate predictors that were significant at $P < .05$ in CI-AKI versus non-CI-AKI univariate analysis and were clinical important were included in the Cox regression models. All data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). A 2-sided *P*-value < .05 was considered significant for all analyses.

3. Results

3.1. Clinical and procedural characteristics

A total of 3065 consecutive patients (76.3% men; mean age, 63 $\pm$ 11 years) who underwent CAG or PCI (emergency PCI, 11.9%) were included in the study, including patients with early single

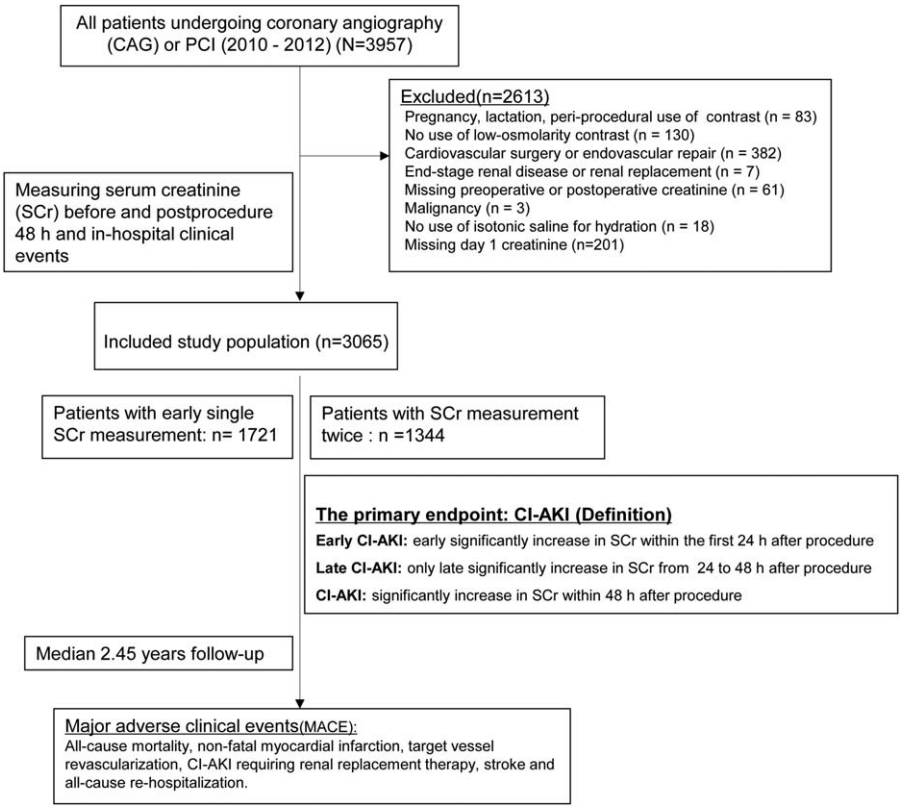

Figure 1. Study flow chart. CAG = coronary angiography, CI-AKI = contrast-induced acute kidney injury, MACE = major adverse clinical events, PCI = percutaneous coronary intervention, SCr = serum creatinine.

SCr measurement after CAG (n = 1721), and patients with both early and late repeat SCr measurements (SCr measured twice; n = 1344; Fig. 1). Compared to patients with SCr measured twice, those with only early single SCr had lower risk factors of CI-AKI, according to the Mehran score (Supplement Table 1, http://links.lww.com/MD/C12).[15] Roughly predicted loss of late CI-AKI in patients with only 1st day SCr using Mehran score was 1.35% (Supplement Table 2, http://links.lww.com/MD/C12). Patients with SCr measured twice had higher incidence of early CI-AKI and mortality, and were more likely to develop MACE and need dialysis in-hospital and during follow-up (Supplement Table 3, http://links.lww.com/MD/C12). Therefore, we primarily studied patients with SCr measured twice in order to evaluate the incidence and predictive value of early single or late repeat SCr increases for long-term mortality after CAG or PCI.

The clinical characteristics of patients with early and late phase CI-AKI are presented in Table 1. Compared to patients with late CI-AKI, those with early CI-AKI had a higher estimated glomerular filtration rate and similar age, rate of diabetes, congestive heart failure, anemia, emergency PCI, and contrast volume. The patients with early CI-AKI received similar hydration/IV fluid (mean, median [interquartile range]: 1128 ± 688, 1000, [500–1500] vs 1087 ± 535, 1000, [600–1290], $P = .861$) to that in patients with late CI-AKI. When early CI-AKI was divided into 2 groups: early CI-AKI$^{\text{normal late}}$ and early CI-AKI$^{\text{abnormal late}}$, the patients with early CI-AKI$^{\text{abnormal late}}$ had old age, worse renal, and heart function and undergoing more emergent PCI than that among patients with early CI-AKI$^{\text{normal late}}$ (Supplement Table 4, http://links.lww.com/MD/C12).

3.2. Definitions of contrast-induced acute kidney injury and in-hospital outcomes

Overall, CI-AKI developed in 134 patients (10%), and the incidence of late and early CI-AKI were 3.6% and 6.4%, respectively. When defining an increase as SCr ≥0.3 mg/dL or ≥50% from baseline was used, and similar results were obtained when using other increase criteria (eg, 0.5/25%, 6.0%, and 9.7%, respectively, $P = .001$; Fig. 2). Patients with early CI-AKI were more likely to develop in-hospital MACE than those with late CI-AKI (39.5% vs 20.8%, $P = .027$), and tended to have higher rates of in-hospital mortality (16.3% vs 8.3%, $P = .196$; Table 2). When early CI-AKI was divided into 2 groups: early CI-AKI$^{\text{normal late}}$ and early CI-AKI$^{\text{abnormal late}}$, the patients with early CI-AKI$^{\text{abnormal late}}$ were more likely to suffered death and other adverse invents than that among patients with early CI-AKI$^{\text{normal late}}$ (Supplement Table 5, http://links.lww.com/MD/C12).

3.3. Long-term outcomes

The long-term mortality (3-year, 29.7% and 35.6%, respectively, $P = .553$) and frequency of MACE (3-year, 44.7% and 57.1% respectively, $P = .226$) were similar between patients with late CI-AKI and patients with early (Table 2). Kaplan–Meier curve analysis revealed that those with early or late CI-AKI had increased mortality, compared to patients without CI-AKI ($P < .001$; Fig. 3). There was significant difference in the patients who get 1 or 2 SCr draws, the patients with SCr measured twice had more risk of mortality (Supplement Figure 1, http://links.lww.com/MD/C12).

Table 1

Clinical characteristics of patients with or without contrast-induced acute kidney injury among patients with serum creatinine measured twice (n = 1344).

		CI-AKI					
	Total (n = 1344)	Total (n = 134)	Early CI-AKI (n = 86)	Late-CI-AKI (n = 48)	*P*	No CI-AKI (n = 1210)	*P*
Age, y	64.18 ± 11.36	70.39 ± 10.07	70.01 ± 10.37	71.06 ± 9.56	.564	63.49 ± 11.29	<.001
Age >75 y	232 (17.3%)	46 (34.3%)	30 (34.9%)	16 (33.3%)	.856	186 (15.4%)	<.001
Men	1054 (78.4%)	98 (73.1%)	64 (74.4%)	34 (70.8%)	.653	954 (79.0%)	.117
Weight, kg	64.30 ± 10.57	61.71 ± 9.87	61.35 ± 10.12	62.34 ± 9.46	.580	64.59 ± 10.61	.003
Smokers	524 (39.0%)	43 (32.1%)	30 (34.9%)	13 (27.1%)	.354	481 (39.8%)	.084
Hypertension	792 (58.9%)	100 (74.6%)	64 (74.4%)	36 (75.0%)	.941	692 (57.2%)	<.001
Diabetes mellitus	348 (25.9%)	43 (32.1%)	25 (29.1%)	18 (37.5%)	.316	305 (25.2%)	.085
Anemia	458 (34.5%)	61 (46.2%)	36 (42.9%)	25 (52.1%)	.306	397 (33.2%)	.003
Hyperlipidaemia	205 (15.3%)	17 (12.7%)	8 (9.3%)	9 (18.8%)	.115	188 (15.5%)	.384
CHF	270 (20.2%)	59 (44.0%)	39 (45.3%)	20 (41.7%)	.681	211 (17.5%)	<.001
Previous MI	159 (11.8%)	17 (12.7%)	12 (14.0%)	5 (10.4%)	.555	142 (11.7%)	.746
Previous CABG	8 (0.6%)	2 (1.5%)	2 (2.3%)	0 (0.0%)	.287	6 (0.5%)	.155
Biochemical parameters							
SBP, mm Hg	129.13 ± 20.75	131.00 ± 25.26	128.76 ± 25.29	135.04 ± 24.95	.172	128.92 ± 20.20	.362
Hypotension	27 (2.0%)	8 (6.1%)	5 (5.9%)	3 (6.4%)	.908	19 (1.6%)	<.001
LVEF	56.30 ± 12.58	51.98 ± 12.80	51.35 ± 12.97	53.14 ± 12.53	.452	56.81 ± 12.46	<.001
LVEF <40%	140 (11.3%)	22 (17.1%)	15 (17.9%)	7 (15.6%)	.740	118 (10.6%)	.029
Baseline serum creatinine, μmol/L	96.89 ± 51.00	120.26 ± 56.69	115.40 ± 58.66	128.95 ± 52.44	.186	94.31 ± 49.69	<.001
24 h serum creatinine, μmol/L	99.39 ± 46.13	158.73 ± 65.96	169.04 ± 70.55	140.26 ± 52.60	.008	92.81 ± 38.10	<.001
48 h serum creatinine, μmol/L	105.44 ± 53.34	183.21 ± 90.61	173.61 ± 107.39	170.94 ± 64.12	.857	170.94 ± 64.12	<.001
Baseline creatinine clearance rate, mL/min	68.47 ± 28.23	52.79 ± 32.59	55.59 ± 33.45	47.78 ± 30.70	.184	70.21 ± 27.17	<.001
Baseline eGFR, mL/min/1.73 m^2	79.22 ± 26.86	66.59 ± 37.33	71.82 ± 41.26	57.23 ± 26.95	.015	80.62 ± 25.07	<.001
HbA1c, %	6.61 ± 1.39	6.77 ± 1.43	6.63 ± 1.11	7.02 ± 1.84	.253	6.60 ± 1.39	.231
HDL-C, mmol/L	0.91 ± 0.30	0.90 ± 0.30	0.87 ± 0.30	0.94 ± 0.30	.381	0.91 ± 0.30	.816
LDL-C, mmol/L	2.62 ± 0.97	2.91 ± 1.16	2.75 ± 1.16	3.16 ± 1.14	.191	2.60 ± 0.95	.058
Medication therapy							
Diuretic	280 (20.8%)	52 (38.8%)	31 (36.0%)	21 (43.8%)	.380	228 (18.8%)	<.001
ACEI/ARB	1204 (89.6%)	115 (85.8%)	73 (84.9%)	42 (87.5%)	.677	1089 (90.0%)	.133
β-Blockers	1130 (84.1%)	90 (67.2%)	58 (67.4%)	32 (66.7%)	.927	1040 (86.0%)	<.001
Calcium channel blockers	230 (17.2%)	26 (19.5%)	13 (15.1%)	13 (27.7%)	.081	204 (16.9%)	.440
Procedure performed							
Emergency PCI	290 (21.6%)	49 (36.6%)	36 (41.9%)	13 (27.1%)	.089	241 (19.9%)	<.001
Lesion number	2.23 ± 1.07	2.52 ± 1.11	2.57 ± 1.00	2.41 ± 1.29	.476	2.20 ± 1.06	<.001
No of stents used	1.76 ± 1.25	1.86 ± 1.35	1.84 ± 1.36	1.89 ± 1.35	.865	1.75 ± 1.24	.349
Total stent length, mm	43.60 ± 33.91	45.95 ± 35.89	47.16 ± 37.37	43.70 ± 33.24	.608	43.34 ± 33.69	.412
Procedural duration, min	77.46 ± 45.51	83.91 ± 49.91	85.23 ± 54.73	81.52 ± 40.22	.661	76.75 ± 44.96	.090
Contrast volume, mL	137.73 ± 66.02	147.35 ± 74.07	148.95 ± 72.28	144.48 ± 77.86	.739	136.67 ± 65.01	.111
H V, mean, median, mL	847 ± 493	1113 ± 637	1128 ± 688	1087 ± 535	.861	817 ± 466	<.001
HV, median, (interquartile range)	700 (500–1000)	1000 (550–1500)	1000 (500–1500)	1000 (600–1290)		500 (500–1000)	

ACEI/ARB = angiotensin converting enzyme inhibitors/angiotensin receptor blocker, CABG = coronary artery bypass grafting, CHF = congestive heart failure, CI-AKI = contrast-induced acute kidney injury, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HV = hydration volume, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention, SBP = systolic blood pressure.

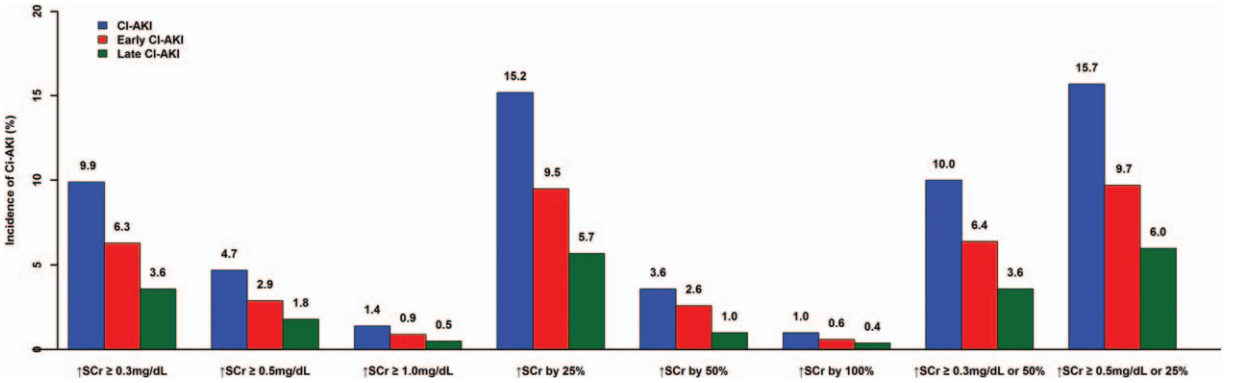

Figure 2. Incidence of CI-AKI according to different criteria in patients with serum creatinine measured twice. Percentage refers to patients with CI-AKI as a percentage of the total population. CI-AKI = contrast-induced acute kidney injury, SCr = serum creatinine.

Table 2

In-hospital and follow-up clinical outcomes for patients with or without CI-AKI in patients with serum creatinine measured twice (n = 1344).

		CI-AKI					
	Total (n = 1344)	Total (n = 134, 10.0%)	Early CI-AKI (n = 86, 6.4%)	Late CI-AKI (n = 48, 3.6%)	P	No CI-AKI (n = 1210, 90.0%)	P
In-hospital outcomes							
Mortality	33 (2.5%)	18 (13.4%)	14 (16.3%)	4 (8.3%)	.196	15 (1.2%)	<.001
MACE	127 (9.4%)	44 (32.8%)	34 (39.5%)	10 (20.8%)	.027	83 (6.9%)	<.001
Acute heart failure	47 (3.5%)	21 (15.7%)	17 (19.8%)	4 (8.3%)	.081	26 (2.2%)	<.001
Re-AMI	7 (0.5%)	4 (3.0%)	3 (3.5%)	1 (2.1%)	.647	3 (0.2%)	<.001
IABP	71 (5.3%)	32 (23.9%)	23 (26.7%)	9 (18.8%)	.298	39 (3.2%)	<.001
Arrhythmia	62 (4.6%)	15 (11.2%)	11 (12.8%)	4 (8.3%)	.433	47 (3.9%)	<.001
Postdialysis	14 (1.0%)	11 (8.2%)	10 (11.6%)	1 (2.1%)	.054	3 (0.2%)	<.001
Stroke	8 (0.6%)	2 (1.5%)	1 (1.2%)	1 (2.1%)	.673	6 (0.5%)	.155
Bleeding	11 (0.8%)	1 (0.7%)	0 (0.0%)	1 (2.1%)	.179	10 (0.8%)	.922
2-y clinical outcomes							
MACE	266 (25.1%)	47 (46.5%)	32 (50.8%)	15 (39.5%)	.269	219 (22.9%)	<.001
Mortality	93 (8.9%)	29 (30.2%)	19 (32.2%)	10 (27.0%)	.591	64 (6.7%)	<.001
Dialysis	15 (1.5%)	11 (12.8%)	10 (18.9%)	1 (3.0%)	.032	4 (0.4%)	<.001
Rehospitalization	160 (15.7%)	12 (15.2%)	8 (17.8%)	4 (11.8%)	.461	148 (15.7%)	.903
TVR	8 (0.8%)	4 (4.9%)	3 (6.5%)	1 (2.9%)	.451	4 (0.4%)	<.001
Stroke	8 (0.8%)	2 (2.5%)	1 (2.2%)	1 (2.9%)	.844	6 (0.6%)	.073
3-y clinical outcomes							
MACE	307 (29.0%)	53 (52.5%)	36 (57.1%)	17 (44.7%)	.226	254 (26.5%)	<.001
Mortality	102 (9.7%)	32 (33.3%)	21 (35.6%)	11 (29.7%)	.553	70 (7.3%)	<.001
Dialysis	15 (1.5%)	11 (12.8%)	10 (18.9%)	1 (3.0%)	.032	4 (0.4%)	<.001
Rehospitalization	193 (18.9%)	15 (19.0%)	10 (22.2%)	5 (14.7%)	.399	178 (18.9%)	.984
TVR	9 (0.9%)	4 (4.9%)	3 (6.5%)	1 (2.9%)	.451	5 (0.5%)	<.001
Stroke	8 (0.8%)	2 (2.5%)	2 (2.5%)	1 (2.2%)	.844	6 (0.6%)	.073

AMI = acute myocardial infarction, CI-AKI = contrast-induced acute kidney injury, MACE = major adverse clinical events, TVR = target vessel revascularization.

In the Cox proportional hazards model, after adjustment for age, hypertension, hypotension, emergent PCI, anemia, CHF, diuretic, renal insufficiency, and lesion number, early CI-AKI (adjusted hazard ratio [HR]: 2.68, 95% confidence interval [CI]: 1.57–4.59, $P < .001$) and late CI-AKI (HR: 2.05, 95% CI: 1.02–4.15, $P = .045$) were significantly associated with mortality (Fig. 4). When using varying criteria to define an increase in SCr (eg, ≥0.3 mg/dL, ≥0.5 mg/dL, ≥25%, and 50%), late and early CI-AKI had similar HRs (Table 3).

We also added 7 other variables (gender, DM, no. of stents used, total stent length, procedural duration, contrast volume, and hydration volume) with significant difference between patients with single and twice SCr measurement, to Cox multivariable analysis and found similar result (Supplement Fig. 2, http://links.lww.com/MD/C12).

When early CI-AKI were divided into 2 groups: early CI-AKI$^{\text{normal late}}$ and early CI-AKI$^{\text{abnormal late}}$, Cox proportional hazards model showed that early CI-AKI$^{\text{abnormal late}}$ (adjusted HR: 3.581, 95% CI): 1.956 to 6.557, $P < .001$) and late CI-AKI (adjusted HR: 2.047, 95% CI): 1.012 to 4.141, $P = .046$) were also significantly associated with increased mortality, while early CI-AKI$^{\text{normal late}}$ (adjusted HR: 1.532, 95% CI: 0.606–3.873,

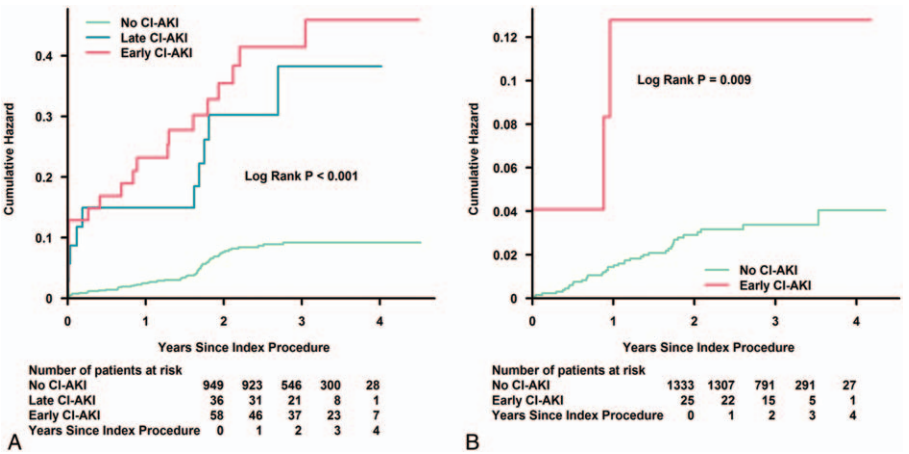

Figure 3. Kaplan–Meier curves for the cumulative probability of mortality stratified according to early, late, and no CI-AKI. Associations between early and late CI-AKI and mortality in patients with SCr measured twice (A) or early single SCr measurement (B). CI-AKI = contrast-induced acute kidney injury, SCr = serum creatinine.

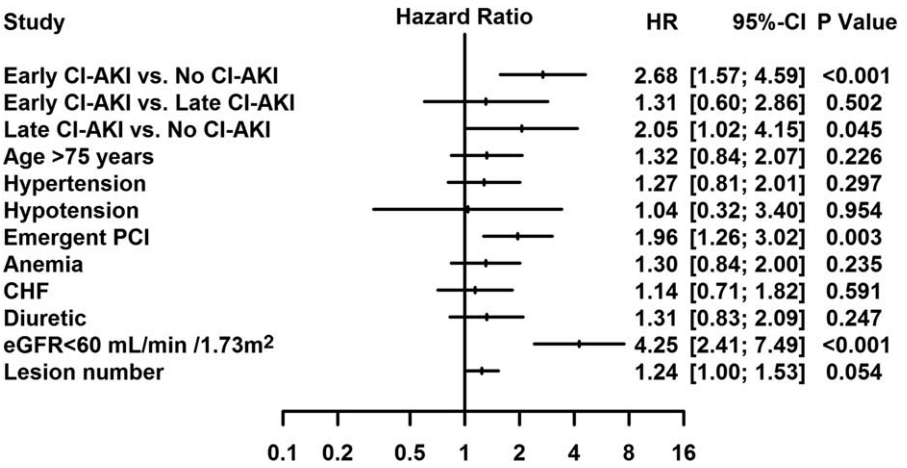

Figure 4. Cox analysis for mortality stratified according to early, late, and no CI-AKI. CHF = congestive heart failure, CI = confidence interval, CI-AKI = contrast-induced acute kidney injury, eGFR = estimated glomerular filtration rate, HR = hazard ratio, PCI = percutaneous coronary intervention.

$P = .367$) did not show an impact on mortality. Further sensitivity analysis showed similar results (Supplement Table 6, http://links.lww.com/MD/C12, Supplement Figure 3, http://links.lww.com/MD/C12).

4. Discussion

To our knowledge, this study may be the first to investigate the distribution and respective clinical significance of different phases of CI-AKI, especially late CI-AKI, which was defined as an increase in SCr that occurred only in the late phase (24–48 hours postprocedure) after CAG or PCI among patients with early and late measurement of SCr. Our data show that late CI-AKI accounts for one third of CI-AKI incidence and its predictive value for long-term mortality was similar to that of early CI-AKI (with 24 hours) after CAG.

SCr is the most commonly used marker for renal function and GFR. Increases in the levels of SCr are associated with subsequent short- and long-term adverse events.[4] After contrast exposure, there is a decline in the excretion of SCr, and the retained SCr is distributed throughout the total body water; thus, the SCr level is expected to slowly rise, continuing to do so until a new steady state has been achieved.[16] Levels of SCr begin to rise within the first 24 hours; typically peak between 2 and 5 days; and return to baseline, or near baseline, within 1 to 3 weeks.[17–19] Recent advances in technology have led to most patients being discharged within 24 hours after CAG or PCI. For those patients, CI-AKI may be underestimated because the late peak value of SCr may occur beyond 24 hours postprocedure. In the present study, most patients who developed CI-AKI experienced the rise to peak SCr in the 1st day, while approximately one third of patients experienced a late (24–48 hours postprocedure) peak; therefore, a prolonged hospital stay to include next-day measurement of SCr would avoid a missed diagnosis of CI-AKI for some patients.[20]

Previous studies showed that minimal elevations of early single SCr (12 hours from baseline) were highly predictive of CI-AKI (increase of SCr >25% in 48 hours).[21] Ribichini et al[22] also found that the early changes in SCr levels (12 hours from baseline) were superior to changes in cystatin C levels for predicting CI-AKI. In the present study, we found that early absolute and relative increases in SCr (within 24 hours) were significantly associated with CI-AKI. Consequently, early increases of SCr (within 24 hours) appear to be a reliable marker for early risk identification of CI-AKI. Laskey et al[8] first defined the early increase in SCr (within 24 hours) as CI-AKI, because post-PCI SCr values were available in 92.8% of patients at 24 hours and in an additional 6.8% from 24 to 48 hours. In real-world clinical practice, the incidence of CI-AKI may be underestimated due to lack of late repeat SCr measurement, between 24 and 48 hours postprocedure. In addition, the prognostic value of the early definition of CI-AKI lacked prognostic values for clinical outcomes has not been assessed in the previous literature. Ribichini et al found that the early increase of SCr (12 hours from baseline) offered better diagnostic accuracy for predicting 30-day renal damage at an early stage, but did not describe long-term adverse clinical outcomes.[21,22] In

Table 3

Mortality associated with varying definitions of increased SCr in patients with serum creatinine measured twice.

	Unadjusted HR* (95% CI)			Multivariable HR* (95% CI)		
Increase in SCr postprocedure	Early CI-AKI	Late CI-AKI	CI-AKI	Early CI-AKI	Late CI-AKI	CI-AKI
↑SCr ≥ 0.3 mg/dL	5.544 (3.360–9.149)	4.141 (2.129–8.053)	4.982 (3.235–7.673)	2.696 (1.574–4.619)	2.055 (1.016–4.153)	2.444 (1.524–3.920)
↑SCr ≥ 0.5 mg/dL	11.271 (6.366–19.955)	4.393 (2.025–9.534)	7.407 (4.564–12.019)	6.557 (3.477–12.366)	1.917 (0.867–4.241)	3.516 (2.084–5.932)
↑SCr ≥ 1.0 mg/dL	13.875 (5.630–34.195)	13.021 (4.115–41.207)	13.542 (6.562–27.946)	9.977 (3.870–25.719)	10.307 (2.959–35.895)	10.083 (4.573–22.229)
↑SCr by 25%	2.753 (1.654–4.584)	2.199 (1.131–4.273)	2.532 (1.637–3.916)	2.253 (1.314–3.862)	1.778 (0.900–3.512)	2.056 (1.300–3.251)
↑SCr by 50%	5.532 (2.678–11.426)	4.604 (1.688–12.558)	5.183 (2.830–9.493)	4.472 (2.035–9.825)	2.986 (1.031–8.650)	3.840 (1.985–7.427)
↑SCr by 100%	7.486 (1.844–30.389)	23.946 (5.868–97.723)	11.397 (4.187–31.028)	5.303 (1.250–22.507)	22.879 (5.017–104.341)	8.758 (3.097–24.767)
↑SCr ≥ 0.3 mg/dL or 50%	5.424 (3.287–8.949)	4.136 (2.127–8.044)	4.915 (3.191–7.569)	2.682 (1.566–4.592)	2.052 (1.015–4.147)	2.435 (1.519–3.904)
↑SCr ≥ 0.5 mg/dL or 25%	2.899 (1.757–4.782)	2.097 (1.078–4.077)	2.570 (1.669–3.958)	2.235 (1.303–3.831)	1.640 (0.832–3.233)	1.977 (1.249–3.130)

↑ Indicates increase. Multivariable analyses were adjusted for age >75 y, hypertension, hypotension, emergent percutaneous coronary intervention, anemia, congestive heart failure, diuretic use, renal insufficiency, and lesion number. CI = confidence interval, CI-AKI = contrast-induced acute kidney injury, HR = hazard ratio, SCr = serum creatinine.

the present study, we found that early CI-AKI was a stronger prognostic indicator for long-term outcomes. In addition, our further analysis showed that the patients with abnormal early and late increase in Scr had worse prognosis than those with abnormal early but normal "somewhat late" increase in Scr, which suggested that more nephrology care should be considered for this group of population.

Although we previously promoted protocol of measuring postangiograph Scr twice (day 1 and 2) for patients in the present study, there are still a considerable number of patients (56%) had a protocol deviation where they were discharged home within 2 days postangiogram. When we compared those with and without twice Scr measurements, we found that the patients with only 1 Scr measurement appeared to be more clinically stable (younger, less hypotensive episodes, intraaortic balloon pump use, and contrast volume use), with less coexistent diseases (better renal and heart function, less anemia, and diabetes) and low risk of clinical outcomes (dialysis or mortality), which may be one of reasons to encourage their treating physicians to discharge them early without repeating Scr measurement in the following day. However, among those with a single Scr measurement, 2.32% patients suffered from early CI-AKI and should have received further monitoring of Scr. In addition, for those without early CI-AKI, further risk stratification (eg, Mehran Score) should be considered to identify patients at high risk of late CI-AKI according to our findings.[15] It appears to be difficult to establish a risk model to predict late CI-AKI for patients without early CI-AKI due to a low event rate of late CI-AKI in the present study.

Our data show that late CI-AKI has predictive value for long-term adverse events, which supports the systematic measurement of SCr until 48 hours postprocedure. The early definition of CI-AKI, on the basis of changes in SCr within 24 hours, may be an early and useful tool for identifying patients who develop CI-AKI; however, the result of our limited data is not power enough to change practice patterns to mandate prolonged hospital stay merely for measuring a late SCr. The present study just wants to call for an attention to the lost of late CI-AKI result by early discharge, and we hope further studies can provide more good predictive tools to give an accurate estimate of the risk of CI-AKI in day 1, day 2, and day 3 or later after contrast exposure to help doctors to decide whether a patient can discharge early or have to prolong hospital stay. The development of a benefit and cost profile of late continuous measurement of SCr requires further larger multicenter clinical research.

4.1. Study limitation

Our study has several limitations. First, variation in the measurement times in each phase may weaken the accuracy of the results. Second, because this prospective observational study was conducted at a single center, a large scale, multicenter randomized controlled trial is needed to evaluate the late measurement of SCr. Third, cardiologists may perform intensive hydration with a higher volume for patients with more risk factors, which may influence the risk of CI-AKI and time period of increase in Scr (early CI-AKI or late CI-AKI). Forth, 56% (1721/3065) patients received only 1 measurement of Scr despite of previously promoted protocol of 2 times (early, <24 hours and late, 24–48 hours) measurement of Scr, which may led to miss to value the true risk of late CI-AKI. These patients with once Scr presented with more clinical stable and less CI-AKI risk factors and tend to receive less clinical care or discharge early. Finally, there was lack of data on Scr beyond 3 days postcoronary angiogram in the present study; however, our study aimed at identification of CI-AKI at the earliest possible time postcontrast exposure.

5. Conclusion

Our data showed a late increase in SCr accounted for about one-third of classical CIN incidence and had similar predictive value for long-term mortality as that for early increase among patients with twice measurement of SCr, supporting the importance of the prolonged measurement of SCr after CAG, even for patients lacking an early significant increase of SCr. In addition, more nephrology care should be considered for the patients with abnormal early and late increase in SCr. However, the benefit and cost profile of late continuous measurement of SCr, which try to get sufficient very late SCr data (eg, 48–72 hours, 2–5 days, or 1–3 weeks), needs to be investigated in further large-scale, multicenter clinical researches.

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