Original Article

Simple pre-procedure risk stratification tool for contrast-induced nephropathy

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Background: A few simple and pre-procedural risk models have been developed for predicting contrast-induced nephropathy (CIN), which allow for early administration of preventative strategies before coronary angiography (CAG). The study aims to develop and validate simple pre-procedure tools for predicting risk of CIN following CAG.

Methods: We retrospectively analyzed the data from 3,469 consecutive patients undergoing CAG, who were randomly assigned to a development dataset (n=2,313) and a validation dataset (n=1,156). CIN was defined as an increase in serum creatinine (SCr) ≥0.5 mg/dL from baseline within 72 hours after CAG. Multivariate logistic regression was applied to identify independent predictors of CIN to develop risk models. The possible predictors included age >75 years, hypotension, acute myocardial infarction (AMI), SCr ≥1.5 mg/dL, and congestive heart failure (CHF).

Results: The incidences of CIN were 3.20% and 3.55% in the training and validation dataset respectively. Compared to classical Mehran' and ACEF CIN risk score, the new score across the validation dataset exhibited similar discrimination and predictive ability on CIN (c-statistic: 0.829, 0.832, 0.812 respectively) and in-hospital mortality (c-statistic: 0.909, 0.937, 0.866 respectively) (all P>0.05).

Conclusions: The easy-to-use pre-procedural prediction model only containing 5 factors had similar predictive ability on CIN and mortality.

Keywords: Contrast-induced nephropathy (CIN); percutaneous coronary intervention; coronary angiography (CAG); risk score

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Introduction

Contrast-induced nephropathy (CIN) has been previously shown to be associated with increased cardiovascular events and mortality following exposure of contrast medium during coronary angiography (CAG) (1,2). Current guidelines recommend intravenous hydration, use of low- or iso-osmolar contrast media, and reduced volume of contrast agents, as prevention strategies for CIN (3,4). Meanwhile, pre-procedural identification of patients at risk for CIN would be of immense value in targeting prophylactic therapy to those at high risk (5).

Studies have reported several models of prediction for CIN following CAG (6,7). However, simple pre-procedural risk models validated by the downstream effects of decision making and patient outcomes have not been explored for clinical guidance (7). Therefore, in the present study, we intended to develop a simple pre-procedure risk model of CIN.

Methods

Study population

According to our institution's protocol, we enrolled consecutive patients undergoing CAG or PCI between January 2010 and October 2012. The details of the inclusion and exclusion criteria were described previously (8,9). The Guangdong General Hospital Ethics Committee approved the study, and written informed consent was obtained from all patients. Finally, 3,469 patients were included in the retrospectively analysis.

Definitions and follow-up

$CIN_{0.5}$ was defined as an elevated serum creatinine (SCr) level >0.5 mg/dL of baseline SCr level within 72 hours after CAG (10). The definitions of anemia, hypotension, and congestive heart failure (CHF) were the same as those in Mehran's study (11).

Follow-up major adverse clinical events (MACEs) were carefully monitored and recorded by trained nurses through office visits and telephone interviews at 1, 6, 12, 24, 36, and 48 months after CAG. MACEs included death, re-nonfatal acute myocardial infarction (re-AMI), target vessel revascularization (TVR), CI-AKI requiring renal replacement therapy (RRT), stroke, and re-hospitalization after index hospitalization.

Model development and model validation

A total of 3,469 eligible patients from the entire database were randomly established into a development dataset (n=2,313) and a validation dataset (n=1,156) in a 2:1 manner. After identifying the associations of clinical baseline and key procedural characteristics with CIN, independent predictors of CIN were analyzed in the development dataset. Risk factors that were significant in the univariate analysis were available for selection in the final mode. Age >75 years, hypotension, acute myocardial infarction (AMI), SCr ≥1.5 mg/dL, CHF were identified as independent pre-procedural predictors of CIN. The risk score was established subsequently and tested in the validation dataset. Model discrimination and its predictive performance for the occurrence of CIN and its short- and long-term outcomes were assessed via comparisons with Mehran's score and ACEF score (12).

Statistical analysis

The association between CIN and variables in the development group was evaluated using univariable logistic regression analysis. A stepwise multivariable logistic regression analysis was then performed to identify independent predictors of CIN. For all logistic regression analysis models, odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. The variables that were independently and significantly associated with CIN in the final multivariable model were assigned a weighted integer coefficient value based upon its beta value. Therefore, a risk score model was constructed where the final risk score for each patient represented the sum of integer coefficients. The risk score was tested in the validation dataset. Model discrimination was assessed by the goodness-of-fit Hosmer-Lemeshow statistic, and its predictive performance was assessed with the c-statistic. Continuous variables were presented as mean ± standard deviation (SD), and as percentages for categorical data. The differences between groups for continuous variables were analyzed by using independent Student's *t*-test. Comparisons between categorical variables were performed with the Pearson χ^2 test or Fisher's exact test. The tendency test of the risk score was analyzed by the Cochran-Armitage trend test. Survival curves were generated with the Kaplan-Meier method, and the differences between groups were assessed by log-rank test. A P<0.05 (2-sided) was considered to indicate statistical significance. The IBM PASW-SPSS Statistics 22.0 statistical

software package (SPSS Inc., Chicago, IL, USA) was used for all calculations with an exception of area under the curve (AUC) comparison for which MedCalc 11.4 Statistical Software (MedCalc Software, Mariakerke, Belgium) was used.

Results

Baseline characteristics

The cumulative incidence of CIN was 115 (3.32%) in the whole study population (n=3,469), with 74 (3.20%) occurring in the development dataset. Overall (*Table 1*), the mean age was 62.9±11.1 years old, and there were 807 (23.3%) females. The mean baseline SCr level was 1.04±0.48 mg/dL, whereas 291 (8.4%) of patients presented creatinine levels≥1.5 mg/dL. Suffering hypotension (20.0% *vs.* 2.0%, P<0.001), anemia, AMI, and CHF also showed significant difference between the CIN group and non-CIN group. Laboratory measurements such as B-type natriuretic peptide (BNP), serum urea nitrogen, and uric acid were remarkably higher in the CIN group when compared with the non-CIN group, along with procedural characteristics contrast volume and hydration volume. There were no intergroup differences in terms of gender and a medical history of previous myocardial infarction (MI), diabetes mellitus (DM), or hyperlipidemia. In addition, the comparison of the baseline clinical and procedural characteristics in the development dataset defined by $CIN_{0.5}$ is listed in *Table 2*.

Univariable logistic regression models and multivariate model

Univariable logistic regression models associated with CIN are shown in *Table 3*. A total of 12 pre-procedural variables were analyzed in the development of CIN. The significant correlates included demographics (age >75 years, weight, and heart rate) and medical history such as hypertension, hypotension, AMI, anemia, CHF, use of IABP as well as history of smoking, and laboratory findings for SCr.

The multivariate model of CIN predictors was obtained from all 2,313 patients in the development dataset with no missing co-variate values. Age >75 years, hypotension, AMI, SCr ≥1.5 mg/dL, and CHF were identified as independent predictors and demonstrated to be markedly associated with CIN (*Table 4*). The Hosmer-Lemeshow statistic for the multivariable model did not suggest a lack of fit (χ^2=4.913, P=0.178).

Development of risk score

The incidence of CIN by risk score assignment is depicted in *Figure 1*, with significant trends across increasing score values for predicting CIN (Cochran Armitage chi-square, P<0.001). Based on the obtained frequencies of CIN in relation to different risk scores, 2,313 patients in the development dataset were further categorized into 3 groups: low risk (n=17, 0.9%), moderate risk (n=31, 8.1%), and high risk (n=26, 27.1%), while corresponding to risk scores of <2, 2 to 3, and ≥4, respectively (*Figure 2*).

Validation and comparison of risk score

CIN occurred in 41 (3.55%) of the 1,156 patients in the validation dataset. The rates of CIN in the validation set presented in parallel to those in the development set inside each of the 3 risk groups (*Figure 2*). The developed CIN model demonstrated similar discriminative power (*Figure 3*) with respect to the incidence of CIN in the validation population (c-statistic =0.829) when compared with Mehran and ACEF score.

The mean follow-up time was 2.31±0.93 years (median, 2.18 years; interquartile range, 1.64–3.04 years). The impacts of short- and long-term outcomes in the development and validation datasets according to risk strata are shown in *Figure 4*, and the comparison of the risk scores on outcomes was also conducted (*Table 5*). The present risk score model as assessed in the validation population by the c-statistic demonstrated an even higher predictive accuracy on outcomes compared to Mehran, ACEF risk scores (*Figure 5*), and the calibration (*Figure 6*). The predictive accuracy for short- and long-term outcomes in the 3 risk scores shows no significant P value, except for in-hospital MACEs (Chen score *vs.* Mehran score, P<0.05). All risk scores performed with excellent discriminative power and with no significant difference for predicting mortality (c statistics: 0.757 to 0.937), especially in-hospital mortality (c statistics: 0.866 to 0.937). In addition, all 3 risk scores also had good predictive accuracy for long-term MACEs with c-statistics ranging from 0.696 (Mehran) to 0.759 (ACEF).

As shown in *Figure 7*, patients with high risk score (≥4) presented with a higher rate of all-cause death than patients with a moderate [2–3] and low risk score (<2) according to log-rank analysis. Significant increases in follow-up

Table 1 Baseline clinical, biochemical, and procedural characteristics in the whole dataset

Characteristic	Total	$CIN_{0.5}$ (n=3,469)		P
		CIN (n=115)	Non-CIN (n=3,354)	
Demographics				
Age, y	62.93±11.138	70.59±10.723	62.66±11.060	<0.001
Age >75 y, n (%)	476 (13.7)	33 (38.3)	432 (12.9)	<0.001
Female sex, n (%)	807 (23.3)	30 (26.1)	777 (23.2)	0.466
Weight, kg	64.889±10.699	61.217±10.181	65.015±10.696	<0.001
SBP, mmHg	128.81±20.412	126.00±27.628	128.91±20.118	0.133
DBP, mmHg	75.93±11.869	73.83±13.650	76.00±11.799	0.055
HR, bpm	75.09±13.367	80.73±18.515	74.89±13.115	<0.001
Medical history				
Diabetes mellitus, n (%)	818 (23.6)	29 (25.2)	789 (23.5)	0.674
Hypertension, n (%)	1,967 (56.7)	79 (68.9)	1,888 (56.3)	0.008
Pre-hypotension, n (%)	91 (2.6)	23 (20.0)	68 (2.0)	<0.001
Hyperlipidemia, n (%)	510 (14.7)	13 (11.3)	497 (14.8)	0.295
Anemia, n (%)	1,089 (31.4)	57 (49.6)	1,032 (30.8)	<0.001
History of smoking, n (%)	1,372 (39.6)	35 (30.4)	1,337 (39.9)	0.042
Previous MI, n (%)	331 (9.5)	9 (7.8)	322 (9.6)	0.524
Previous CABG, n (%)	27 (0.8)	0 (0.0)	27 (0.8)	0.334
AMI, n (%)	1,312 (37.8)	78 (67.8)	1,234 (36.8)	<0.001
LVEF, %	57.775±12.272	49.304±14.109	58.074±12.097	<0.001
LVEF <40%, n (%)	295 (9.8)	24 (23.3)	271 (9.3)	<0.001
Pre-IABP, n (%)	16 (0.5)	4 (3.5)	12 (0.4)	<0.001
Heart function, n (%)				
Killip class >1	539 (15.5)	59 (51.3)	480 (14.3)	<0.001
NYHA class >1	1,880 (54.2)	84 (86.6)	1,796 (68.2)	<0.001
NYHA class >2	521 (15.0)	58 (50.4)	463 (13.8)	<0.001
Laboratory measurements				
Hemoglobin, g/L	132.988±16.335	121.556±24.177	133.306±15.952	<0.001
BNP, pg/mL	2.478±0.800	3.413±0.750	2.448±0.784	<0.001
Serum urea nitrogen, mg/dL	5.287±2.538	8.277±4.447	5.184±2.382	<0.001
Serum albumin, g/L	35.218±7.053	30.547±4.898	35.348±7.061	<0.001
Uric acid, mmol/L	377.429±110.092	460.748±150.117	374.427±107.212	<0.001
LDL-C, mmol/L	2.689±0.987	2.736±1.103	2.688±0.984	0.712
HDL-C, mmol/L	0.927±0.288	0.846±0.274	0.928±0.288	0.099
Total cholesterol, mmol/L	4.461±1.144	4.468±1.472	4.461±1.134	0.960
Serum cystatin C, ng/mL	1.225±0.545	1.858±0.833	1.215±0.534	<0.001
HbA1c, %	6.538±1.321	6.649±1.180	6.534±1.325	0.438

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Total	$CIN_{0.5}$ (n=3,469)		P
		CIN (n=115)	Non-CIN (n=3,354)	
SCr, mg/dL	1.044±0.478	1.571±0.769	1.026±0.454	<0.001
SCr ≥1.5 mg/dL, n (%)	291 (8.4)	46 (40.0)	245 (7.3)	<0.001
CrCl, mL/min	74.473±28.522	46.718±25.994	75.425±28.126	<0.001
CrCl class, n (%)				
≤30	122 (3.5)	33 (28.7)	89 (2.7)	<0.001
30–60	991 (28.6)	52 (45.2)	939 (28.0)	<0.001
60–90	1,486 (42.8)	22 (19.1)	1,464 (43.6)	<0.001
>90	870 (25.1)	8 (7.0)	862 (25.7)	<0.001
eGFR, mL/min/1.73 mm^2	81.447±25.673	55.706±28.088	82.329±25.127	<0.001
Medication, n (%)				
ACEI/ARB	3,032 (87.4)	85 (73.9)	2,947 (87.9)	<0.001
β-blocker	2,934 (84.6)	71 (61.7)	2,863 (85.4)	<0.001
CCB	595 (17.2)	17 (14.8)	578 (17.2)	0.493
Diuretics	656 (18.9)	56 (48.7)	600 (17.9)	<0.001
Statin	3,328 (95.9)	104 (90.4)	3,224 (96.1)	0.002
Metformin	82 (2.6)	0 (0.0)	82 (2.7)	0.130
Procedure performed				
Coronary lesion, n (%)	2,702 (88.0)	81 (97.6)	2,621 (87.7)	0.006
Length of stents, mm	47.64±30.678	49.53±32.879	47.58±30.610	0.597
Number of stenting, n	1.88±1.071	1.85±0.967	1.89±1.075	0.769
Coronary stenting, n (%)	2,564 (92.7)	93 (86.1)	2,471 (93.0)	0.007
Contrast type, n (%)				
Iopamidol, iso-osmia	1,907 (55.0)	65 (56.5)	1,842 (54.9)	0.734
Non-iopamidol, anisosmotic	1,562 (45.0)	50 (43.5)	1,512 (45.1)	0.734
Contrast volume, mL	126.57±64.512	139.22±64.779	126.13±64.468	0.032
Vein HV, mL	787.051±478.417	1273.548±916.302	770.370±446.980	<0.001
Peri-hypotension, n (%)	130 (3.7)	31 (27.0)	99 (3.0)	<0.001
Peri-IABP, n (%)	137 (3.9)	40 (34.8)	97 (2.9)	<0.001
Mehran risk score	5.32±4.442	12.81±6.169	5.07±4.138	<0.001
Mehran risk level, n (%)				
Low	2,208 (63.6)	15 (13.0)	2,193 (65.4)	<0.001
Middle	852 (24.6)	25 (21.7)	827 (24.7)	<0.001
High	276 (8.0)	35 (30.4)	241 (7.2)	<0.001
Very high	133 (3.8)	40 (34.8)	93 (2.8)	<0.001

MI, myocardial infarction; CABG, coronary artery bypass grafting; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; CrCl, creatinine clearance; ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blocker; CCB, calcium channel blocker; IABP, intra-aortic balloon pump.

Table 2 Baseline clinical, biochemical, and procedural characteristics in the development dataset

Characteristic	Total	$CIN_{0.5}$ (n=2,313)		P
		CIN (n=74)	Non-CIN (n=2,239)	
Demographics				
Age, y	62.58±11.199	70.50±10.826	62.32±11.117	<0.001
Age >75 y, n (%)	299 (12.9)	29 (39.2)	270 (12.1)	<0.001
Female sex, n (%)	538 (23.3)	21 (28.4)	517 (23.1)	0.289
Weight, kg	64.786±10.796	61.649±10.891	64.889±10.779	0.011
SBP, mmHg	128.88±20.638	127.54±28.536	128.92±20.332	0.570
DBP, mmHg	75.91±11.813	73.61±14.113	75.98±11.726	0.089
HR, bpm	75.20±13.382	78.58±17.484	75.09±13.215	0.027
Medical history				
Diabetes mellitus, n (%)	545 (23.6)	17 (23.0)	528 (23.6)	0.903
Hypertension, n (%)	1,301 (56.2)	51 (68.9)	1,250 (55.8)	0.026
Pre-hypotension, n (%)	62 (2.7)	16 (21.6)	46 (2.1)	<0.001
Hyperlipidemia, n (%)	350 (15.1)	9 (12.2)	341 (15.2)	0.469
Anemia, n (%)	713 (30.8)	37 (50.0)	676 (30.2)	0.099
History of smoking, n (%)	933 (40.3)	21 (28.4)	912 (40.7)	<0.001
Previous MI, n (%)	229 (9.9)	7 (9.5)	222 (9.9)	0.897
AMI, n (%)	868 (37.5)	51 (68.9)	817 (36.5)	<0.001
Previous CABG, n (%)	17 (0.7)	0 (0.0)	17 (0.8)	0.452
LVEF, %	57.798±12.291	50.183±13.808	58.052±12.160	<0.001
LVEF <40%, n (%)	198 (9.8)	12 (18.5)	186 (9.5)	0.018
Pre-IABP, n (%)	12 (0.5)	3 (4.1)	9 (0.4)	<0.001
Heart function, n (%)				
Killip class >1	359 (15.5)	35 (47.3)	324 (14.5)	<0.001
NYHA class >1	1,250 (68.8)	52 (82.5)	1,198 (68.3)	0.016
NYHA class >2	343 (14.8)	35 (47.3)	308 (13.8)	<0.001
Laboratory measurements				
Hemoglobin, g/L	133.428±16.248	121.180±24.181	133.773±15.841	<0.001
BNP, pg/mL	2.478±0.809	3.404±0.773	2.448±0.793	0.009
Serum urea nitrogen, mg/dL	5.291±2.658	8.448±4.616	5.186±2.503	<0.001
Serum albumin, g/L	35.339±7.975	31.215±4.462	35.456±8.022	<0.001
Uric acid, mmol/L	376.838±110.326	463.833±143.144	373.859±107.844	<0.001
LDL-C, mmol/L	2.676±0.981	2.556±1.137	2.679±0.977	0.446
HDL-C, mmol/L	0.928±0.292	0.811±0.300	0.930±0.292	0.053
Total cholesterol, mmol/L	4.459±1.129	4.154±1.311	4.467±1.124	0.092
Serum cystatin C, ng/mL	1.239±0.581	1.860±0.848	1.227±0.568	<0.001
HbA1c, %	6.541±1.318	6.666±1.011	6.538±1.326	0.484

Table 2 (*continued*)

Table 2 (*continued*)

Characteristic	Total	$CIN_{0.5}$ (n=2,313)		P
		CIN (n=74)	Non-CIN (n=2,239)	
SCr, mg/dL	1.043±0.447	1.536±0.697	1.027±0.459	<0.001
SCr ≥1.5 mg/dL, n (%)	198 (8.6)	31 (41.9)	167 (7.5)	<0.001
CrCl, mL/min	74.796±28.695	47.869±27.723	75.686±28.299	<0.001
CrCl class, n (%)				
≤30	87 (3.8)	21 (28.4)	66 (2.9)	<0.001
30–60	634 (27.4)	33 (44.6)	601 (26.8)	<0.001
60–90	1,006 (43.5)	15 (20.3)	991 (44.3)	<0.001
>90	586 (25.3)	5 (6.8)	581 (25.9)	<0.001
eGFR, mL/min/1.73 mm^2	81.607±25.679	56.054±29.432	82.451±25.113	<0.001
Medication, n (%)				
ACEI/ARB	2,027 (87.6)	56 (75.7)	1,971 (88.0)	<0.001
β-blocker	1,973 (85.3)	48 (64.9)	1,925 (86.0)	<0.001
CCB	380 (16.4)	12 (16.2)	368 (16.4)	0.960
Diuretics	451 (19.5)	34 (45.9)	417 (18.6)	<0.001
Statin	2,226 (96.2)	69 (93.2)	2,157 (96.3)	0.169
Metformin	57 (2.8)	0 (0.0)	57 (2.8)	0.210
Procedure performed				
Coronary lesion, n (%)	1,803 (88.0)	54 (98.2)	1,749 (87.8)	0.019
Length of stents, mm	47.33±30.594	53.51±33.763	47.13±30.476	0.151
Number of stenting, n	1.88±1.066	1.97±1.040	1.87±1.067	0.490
Coronary stenting, n (%)	1,729 (93.2)	61 (87.1)	1,668 (93.4)	0.040
Contrast type, n (%)				
Iopamidol, iso-osmia	1,280 (55.3)	46 (62.2)	1,234 (55.1)	0.230
Non-iopamidol, anisosmotic	1,033 (44.7)	28 (37.8)	1,005 (44.9)	0.230
Contrast volume, mL	126.92±63.845	138.78±57.795	126.53±64.009	0.104
Hydration volume, mL	784.205±464.820	1269.068±901.145	768.180±434.377	<0.001
Peri-hypotension, n (%)	89 (3.8)	22 (29.7)	67 (3.0)	<0.001
Peri-IABP, n (%)	94 (4.1)	26 (35.1)	68 (3.0)	<0.001
Mehran risk score	5.29±4.493	12.82±5.969	5.05±4.214	<0.001
Mehran risk level, n (%)				
Low	1,470 (63.6)	10 (13.5)	1,460 (65.2)	<0.001
Middle	570 (24.6)	17 (23.0)	553 (24.7)	<0.001
High	180 (7.8)	21 (28.4)	159 (7.1)	<0.001
Very high	93 (4.0)	26 (35.1)	67 (3.0)	<0.001

MI, myocardial infarction; CABG, coronary artery bypass grafting; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; CrCl, creatinine clearance; ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blocker; CCB, calcium channel blocker; IABP, intra-aortic balloon pump.

Table 3 Association of baseline, clinical, pre-procedural characteristics and CIN in the development dataset (univariate analysis)

Variable	Patients (%)	Incidence of CIN (%)	OR	CI	P value
Age >75 years	12.9	39.19	4.700	2.897–7.624	<0.001
Weight	N/A	N/A	0.971	0.950–0.993	0.011
Heart rate	N/A	N/A	1.017	1.002–1.033	0.026
DM	23.6	22.97	0.966	0.577–1.676	0.903
Hypertension	56.2	68.92	1.754	1.065–2.890	0.027
AMI	37.5	68.91	3.859	2.341–6.361	<0.001
Pre-hypotension	2.7	21.26	13.151	7.034–24.589	<0.001
Pre-IABP	0.5	4.05	10.469	2.775–39.500	<0.001
Anemia	30.8	50.0	2.312	1.453–3.679	<0.001
SCr ≥1.5 mg/dL	8.6	41.89	8.945	5.491–14.571	<0.001
CHF	14.8	47.30	5.559	3.472–8.901	<0.001
Smoking	40.3	28.38	0.577	0.345–0.962	0.035

CI, confidence interval; OR, odds ratio; CIN, contrast-induced nephropathy; DM, diabetes mellitus; AMI, acute myocardial infarction; IABP, intra-aortic balloon pump; CHF, congestive heart failure.

Table 4 Multivariate predictors of CIN after emergent PCI in development dataset

Variable	Model coefficient (β value)	OR	CI	P value	Integer score
Age >75 years	1.176	3.242	1.902–5.527	<0.001	1
Pre-hypotension	1.904	6.712	3.234–13.930	<0.001	2
AMI	0.835	2.306	1.329–4.000	0.003	1
SCr ≥1.5 mg/dL	1.746	5.731	3.359–9.779	<0.001	2
CHF	0.883	2.417	1.424–4.104	<0.001	1

The Hosmer-Lemeshow statistic was chi-square =4.913 (P=0.178). Risk score strata: 0–1= low risk; 2–3= moderate risk; ≥4= high risk. CI, confidence interval; OR, odds ratio; CIN, contrast-induced nephropathy; AMI, acute myocardial infarction; CrCl, creatinine clearance; CHF, congestive heart failure.

mortality rate were observed with increment of risk score (χ^2=89.23, P<0.001).

Discussion

According to retrospective analysis of the single center data among patients undergoing CAG, we established one simple and precise CIN risk assessment tool with pre-procedural key variables including old age, high SCr, hypotension, CHF, and AMI. Compared to classical Mehran and ACEF scores, the new, simple, and pre-procedural risk score across the validation dataset exhibited similar discrimination and predictive ability for the risk of CIN and mortality.

With the growing trend towards minimally invasive diagnostic and interventional procedures with contrast, there has been a concomitant rise in the incidence of CIN (10). CINs have been associated with increased risk of adverse clinical outcomes, including more complex complications and death (1). Because we lack effective therapies for CIN, the establishment of useful prediction models for CIN would be important and instrumental in prevention. Many studies searching for a prediction model of CIN were performed worldwide in an attempt to help identify those patients at high risk who might benefit from peri-procedural strategies that protect the kidney or improve pre-intervention counseling (11,13-21). In a recent systematic review, models using preprocedural variables performed decently with similar results to those

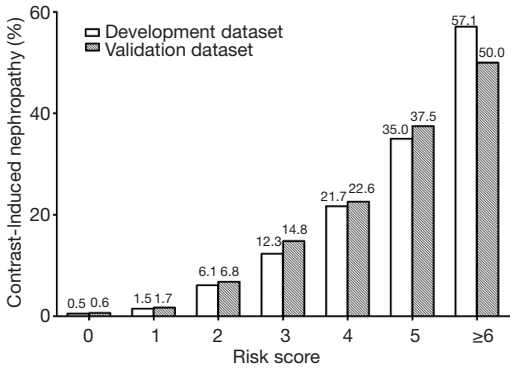

Figure 1 Incidence of contrast induced nephropathy according to the risk score. Increasing risk of CIN with increasing risk score is evident, Cochran Armitage chi-square, P<0.001. CIN, contrast-induced nephropathy.

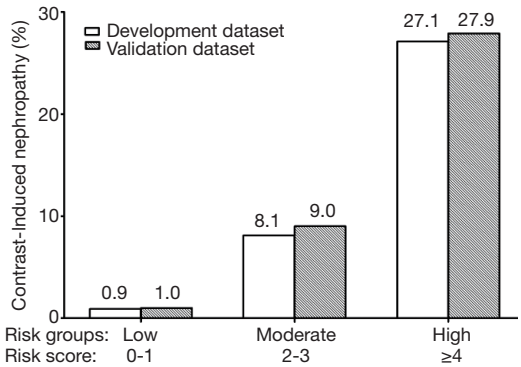

Figure 2 Incidence of contrast induced nephropathy in the development and validation datasets according to risk strata.

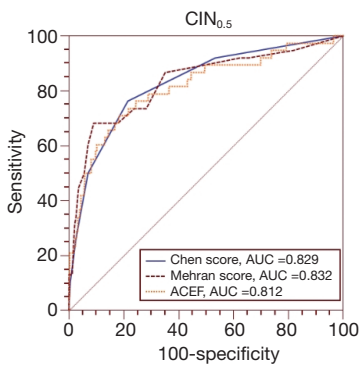

Figure 3 Comparison of predictive accuracy of CIN risk score models between Chen score, Mehran score and ACEF score in $CIN_{0.5}$ (validation dataset). CIN, contrast-induced nephropathy.

of models that incorporated post-procedural variables (22). Our pre-procedure also showed good performance despite lacking post-procedural variables. Chen *et al.* established 1 preprocedural score for risk of CIN after PCI with good predictive value (c-statistic: 0.82), but the score system included 9 variables, which was more complex than ours. Risk factors lacking the validation and improvement of downstream effects make it challenging for a clinician to select the ideal model in practice. Further research is needed to evaluate the effect of their implementation in clinical care.

Most CIN risk models were developed with definitions of $CIN_{0.5}$ (increase ≥0.5 mg/dL in SCr) and CIN_{25} (increase ≥25% and/or >0.5 mg/dL in SCr) (11,13-21,23). A large collaborative registry that included 58 957 patients undergoing PCI suggested that the definition of CIN (increase ≥0.5 mg/dL) is superior to ≥25% increase in SCr for identifying patients at a greater risk of adverse renal and cardiac events among patients undergoing PCI (20). In addition, the combined CIN (increase of ≥25% or absolute 0.5 mg/dL creatinine levels) was not significantly correlated with long-term mortality in patients without CKD (21). Therefore, we chose $CIN_{0.5}$ (increase ≥0.5 mg/dL in SCr) as the endpoint for a risk model with more prognosis value

Advanced age and worse renal function (CKD) were common risk factors for CIN following CAG (11). Recent studies showed that adequate hydration appeared to have a very low risk of CIN following angiography among patients with CKD and CHF. The HYDRA Study showed that evaluation of pre-procedural hydration status allowed higher volume expansion with reduced risk of CIN; thus, a personalized hydration volume could be a more reasonable strategy for the prevention of CIN in the future (24,25). Among patients with CHF, renal vasoconstriction and medullary hypoxia play an important role in the development of CIN. In addition, the effective circulatory volumes are lower in patients who have diminished left ventricular function. The patients were likely to have kidney hypoperfusion with hemodynamic instability, high degree of inflammatory status in the body, along with an inflammation status, endothelial dysfunction, and oxidative stress, that were contributing to the development of CIN. Our new score also included AMI as an independent predictor of CIN following CAG (19,26).

The patients with diabetic nephropathy undergoing

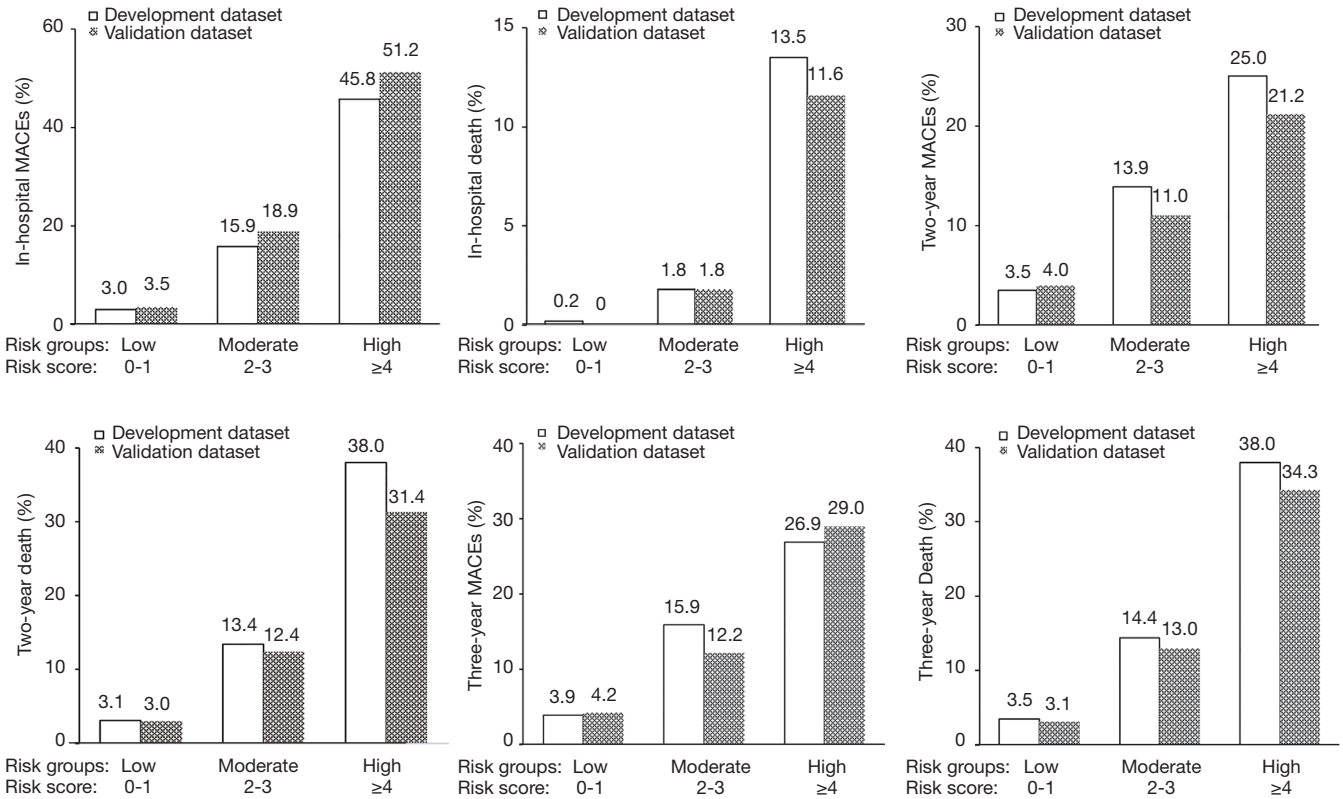

Figure 4 Risk score and short-and long-term outcomes. Rates of in-hospital death and MACEs, 2- and 3-year all-cause mortality and MACEs, in the low-, moderate-, and high-risk groups were showed according to the Chen, Mehran, ACEF risk scores. MACE, major adverse clinical event.

CAG had a very high risk of developing CIN (27). Assareh's study also found that CIN is a common problem in patients with diabetic nephropathy undergoing CAG (28). Peripheral arterial disease (PAD) was also considered as a risk factor (6,15,16), but it did not appear to be associated with CIN in our data, which is more consistent with Mehran and Gurm's studies (11,18).

Limitations

Several limitations exist in the present study. First, since this prospective, observational study was conducted in a single center, further research is needed to evaluate the effect of their implementation in clinical care. Secondly, the CrCl was calculated with the Cockcroft-Gault formula, rather than measured directly. Thirdly, variations in our measurement times might have given rise to missing post-procedure peak SCr levels. Furthermore, half of the patients were discharged 3 days after the CAG, so Scr concentrations were not measured on day 3 in these patients. Variation in the measurement times may have led to overlooked peak levels of the SCr post procedure, which may have also led to an underestimation of the true incidence of CIN in the current study population. At last, poor patient compliance led to a high rate of follow-up loss, which may have affected the results about clinical adverse outcomes during follow-up, and may have influenced the significance of the analysis.

Conclusions

The present study established a simple risk score, which included only 5 key pre-procedural variables with excellent predictive and high discriminative ability, even when compared with classical Mehran and ACEF score, for predicting CIN and short- and long-term outcome in patients before CAG. This could benefit timely administration of pre-procedural preventions. However, the value of the pre-procedural risk model needs to be evaluated in large scale multicenter trials in the future.

Table 5 Predictive accuracy of Chen, Mehran and ACEF risk score

Events	AUC (95% CI)		
	Chen score	Mehran score	ACEF score
$CIN_{0.5}$	0.829 (0.804–0.851)	0.832 (0.807–0.854)	0.812 (0.787–0.836)
In-hospital mortality	0.909 (0.889–0.926)	0.937 (0.920–0.951)	0.866 (0.843–0.886)
In-hospital MACEs	0.801 (0.775–0.825)	0.752 (0.724–0.779)	0.759 (0.732–0.785)
2-year mortality	0.757 (0.726–0.786)	0.777 (0.746–0.805)	0.808 (0.779–0.835)
2-year MACEs	0.715 (0.683–0.746)	0.696 (0.663–0.728)	0.736 (0.704–0.766)
3-year mortality	0.762 (0.731–0.791)	0.788 (0.758–0.816)	0.816 (0.787–0.842)
3-year MACEs	0.730 (0.698–0.761)	0.715 (0.682–0.746)	0.759 (0.728–0.788)

$CIN_{0.5}$: Chen score *vs.* Mehran score, P=0.905; Chen score *vs.* ACEF, P=0.696; Mehran score *vs.* ACEF score, P=0.650. In-hospital mortality: Chen score *vs.* Mehran score, P=0.216; Chen score *vs.* ACEF, P=0.428; Mehran score *vs.* ACEF score, P=0.289. In-hospital MACEs: Chen score *vs.* Mehran score, P=0.046; Chen score *vs.* ACEF, P=0.111; Mehran score *vs.* ACEF score, P=0.825. 2-year mortality: Chen score *vs.* Mehran score, P=0.460; Chen score *vs.* ACEF, P=0.117; Mehran score *vs.* ACEF score, P=0.388. 2-year MACEs: Chen score *vs.* Mehran score, P=0.531; Chen score *vs.* ACEF, P=0.577; Mehran score *vs.* ACEF score, P=0.292. 3-year mortality: Chen score *vs.* Mehran score, P=0.325; Chen score *vs.* ACEF, P=0.088; Mehran score *vs.* ACEF score, P=0.413. 3-year MACEs: Chen score *vs.* Mehran score, P=0.587; Chen score *vs.* ACEF, P=0.400; Mehran score *vs.* ACEF score, P=0.201. CI, confidence interval; CIN, contrast induced nephropathy; MACE, major adverse clinical event.

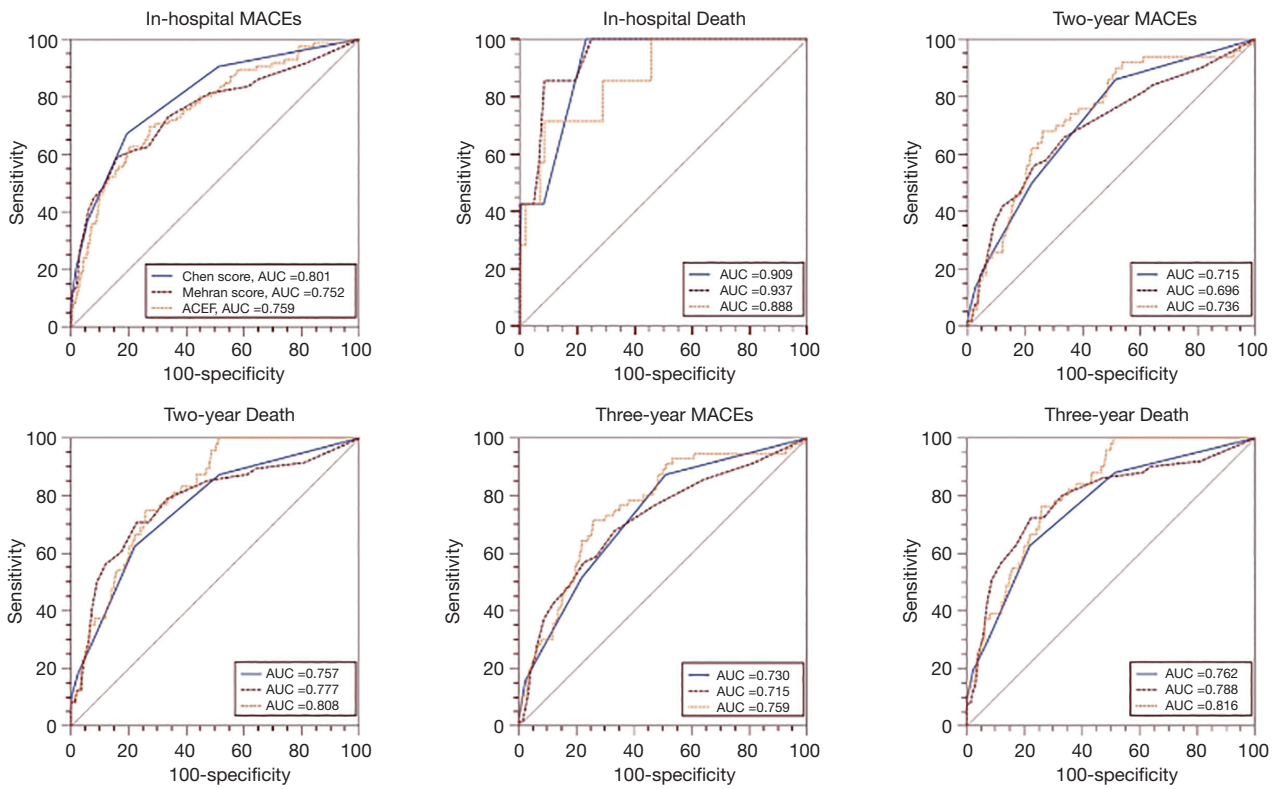

Figure 5 Predictive ability of the risk scores for in-hospital death and MACEs, 2- and 3-year all-cause mortality and MACEs by Chen, Mehran, ACEF risk scores. MACE, major adverse clinical event.

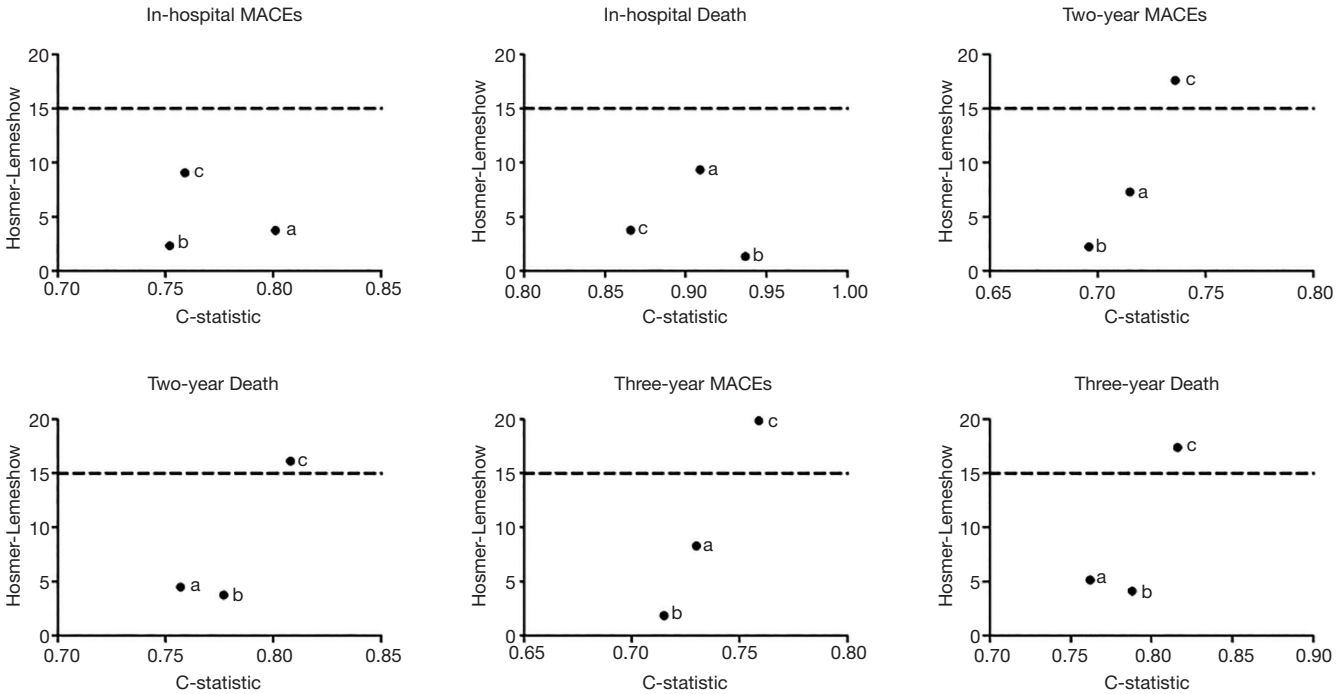

Figure 6 Discrimination (c-statistic) and calibration (HosmereLemeshow test) for Chen score, Mehran score and ACEF score. a = Chen score; b = Mehran score; c = ACEF score.

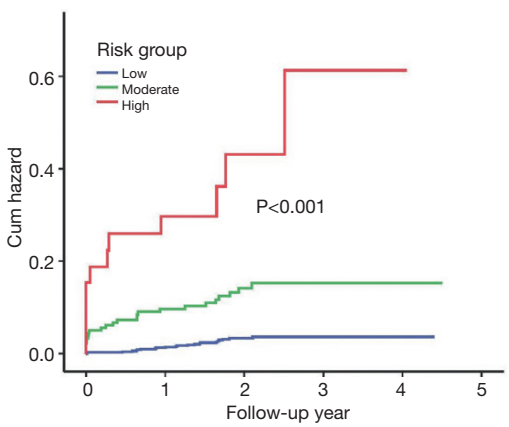

Figure 7 Cumulative mortality as a function of time for patients with low, medium, and high present risk score. Chi-square =89.229, P<0.001.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by The Guangdong General Hospital Ethics Committee and written informed consent was obtained from all patients.

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