

# Dynamic Predictive Scores for Cardiac Surgery–Associated Acute Kidney Injury

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**Background**—Cardiac surgery–associated acute kidney injury (CSA-AKI) is a common complication with a poor prognosis. In order to identify modifiable perioperative risk factors for AKI, which existing risk scores are insufficient to predict, a dynamic clinical risk score to allow clinicians to estimate the risk of CSA-AKI from preoperative to early postoperative periods is needed.

**Methods and Results**—A total of 7233 cardiac surgery patients in our institution from January 2010 to April 2013 were enrolled prospectively and distributed into 2 cohorts. Among the derivation cohort, logistic regression was used to analyze CSA-AKI risk factors preoperatively, on the day of ICU admittance and 24 hours after ICU admittance. Sex, age, valve surgery combined with coronary artery bypass grafting, preoperative NYHA score >2, previous cardiac surgery, preoperative kidney (without renal replacement therapy) disease, intraoperative cardiopulmonary bypass application, intraoperative erythrocyte transfusions, and postoperative low cardiac output syndrome were identified to be associated with CSA-AKI. Among the other 1152 patients who served as a validation cohort, the point scoring of risk factor combinations led to area under receiver operator characteristics curves (AUROC) values for CSA-AKI prediction of 0.74 (preoperative), 0.75 (on the day of ICU admission), and 0.82 (postoperative), and Hosmer–Lemeshow goodness-of-fit tests revealed a good agreement of expected and observed CSA-AKI rates.

**Conclusions**—The first dynamic predictive score system, with Kidney Disease: Improving Global Outcomes (KDIGO) AKI definition, was developed and predictive efficiency for CSA-AKI was validated in cardiac surgery patients. (*J Am Heart Assoc.* 2016;5:e003754 doi: 10.1161/JAHA.116.003754)

**Key Words:** acute kidney injury • cardiac surgery • risk factor • risk score

Acute kidney injury (AKI) is a common complication after cardiac surgery, with reported incidences between 8.9% and 39% as well as mortality of 3.8% to 54.4%, and even slight renal function changes were reported to affect short- and long-term outcome after cardiac surgery.<sup>1–3</sup> Because early prediction in those patients at high risk of developing cardiac surgery–associated acute kidney injury (CSA-AKI) may enable

prevention of complications, in the last 2 decades various predictive models have been developed to forecast CSA-AKI or renal replacement therapy (RRT)-AKI after cardiac surgery,<sup>4–9</sup> in which adequate predictive power was validated among whites.<sup>10,11</sup> However, by now, the predictive value for estimating AKI, RRT-AKI, or death incidence of 5 established models, including the method published by Palomba et al,<sup>7</sup> the Cleveland Clinic score,<sup>8</sup> the scoring system published by Mehta et al,<sup>6</sup> the simplified renal index score,<sup>9</sup> and the EURO score<sup>12</sup> in other racial cohorts after cardiac surgery is uncertain. Possible reasons might include the following. (1) There was no consensus in the definition of AKI when those models were developed. In the AKICS score, AKI was defined as “an increase of serum creatine (Cr) levels above 2.0 mg/dL in patients with baseline serum Cr lower than 1.5 mg/dL.” In patients with baseline serum Cr between 1.5 and 3.0 mg/dL, AKI was defined as “a serum Cr increase of 50% over the baseline value.” In the new 2012 Kidney Disease: Improving Global Outcomes (KDIGO) AKI definition,<sup>13</sup> urine output, as another indicator besides serum creatine, was not utilized to define AKI in Palomba’s study, and AKI may be missed. (2) With the recognition of intraoperative and postoperative risk

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factors, especially the modifiable factors, contributing to CSA-AKI, risk scores<sup>6,8,9</sup> including only preoperative risk factors can hardly meet the predictive requirement. (3) In some developing countries such as China, the proportions of valve surgery, comorbidities, and population race<sup>14</sup> are quite different from those of the existing model derivation cohorts. With the development of medical technology, cardiac surgery in developing countries is booming. Meanwhile complications of surgery and economic burdens are also increasing due to restriction of medical technology and management. We aimed to develop a dynamic predictive model for CSA-AKI based on the recent KDIGO AKI definition, which was devised to predict the incidence of CSA-AKI from preoperative to early postoperative periods and to validate its predictive capacity for improved clinical application.

## Patients and Methods

### Patients

In our prospective study we included 7233 patients who were divided into a derivation cohort (6081 patients between January 2010 and October 2012) and a validation cohort (1152 patients between November 2012 and April 2013); all were admitted to the Zhongshan Hospital, Shanghai Medical College, Fudan University. The study was approved by the ethical committee of the Zhongshan Hospital, and all participants provided written informed consent.

Inclusion criteria were adult patients who underwent coronary artery bypass grafting (CABG), off-pump coronary artery bypass (OPCAB), valve surgery, or valve combined with CABG surgery. Excluded were patients with previous heart transplantation, preoperative mechanical ventilation or tracheotomy, preoperative defibrillator or ventricular assist devices, preoperative RRT, preoperative liver dysfunction, or sepsis.

### Data Collection

The clinical characteristics of both derivation and validation cohorts have been collected and were extracted from the database of Zhongshan Hospital cardiac surgery. All data were checked twice by medical personnel (postgraduate and resident doctor) before being admitted to the database. We collected data including sex, age, weight, length of stay, length of ICU stay, and outcome; preoperative data including diagnosis, comorbidities including hypertension, diabetes mellitus, atrial fibrillation, endocarditis, coronary artery disease, cerebral vascular disease, anemia, chronic obstructive pulmonary disease, kidney disease without renal replacement therapy; and laboratory reports including estimated glomerular filtration rate (eGFR), which were calculated with CKD-EPI formulas,<sup>15</sup> in addition to New York Heart

Association (NYHA) functional classification, left ventricular ejection fraction (LVEF), preoperative congestive heart failure, preoperative intra-aortic balloon pump (IABP), previous cardiac surgery history, recent contrast media (CM) exposure, and renal toxic drug exposure. Intraoperative data included emergency surgery, procedure type, cardiopulmonary bypass (CPB) application and time, transfusion, and fluid balance; postoperative data comprised low cardiac output syndrome (LCOS), central venous pressure, medicine application, mechanical ventilation, RRT, and renal recovery. AKI was defined according to the KDIGO guideline<sup>13</sup> as any of the following: increase in SCr by  $\geq 0.3$  mg/dL ( $\geq 26.5$   $\mu\text{mol/L}$ ) within 48 hours; or increase in SCr to  $\geq 1.5$  times baseline that is known or presumed to have occurred within the prior 7 days or urine volume  $< 0.5$  mL/kg per hour for 6 hours. If there were more than 1 cardiac surgery procedures performed during the same hospitalization, only the data on the first surgery were considered. If there were more than 1 hospitalization between January 2010 and April 2013, only the data on the first hospitalization were considered.

### Statistical Analyses

Statistical analyses were carried out by SPSS statistics for Windows (Version 20.0. IBM Corp, Armonk, NY). Continuous variables were expressed as mean $\pm$ SD and analyzed by unpaired t tests, with Welch adjustment when necessary. Continuous variables that violated the normality assumption were expressed as median and 25th to 75th percentiles and analyzed by a Mann-Whitney U test. Categorical variables were expressed as absolute (n) and relative (%) frequency and were analyzed by the Pearson 2-test or the Fisher exact test whenever appropriate. Significant level was considered with  $P < 0.05$ . Univariate analysis was carried out for patient data, and multivariate analysis by logistic regression was used to obtain data about the risk factors for AKI at the 3 time points: preoperative, ICU admittance, and 24 hours after ICU admittance. In the multivariate analysis, results were expressed by the odds ratio and the 95% confidence interval. The regression  $\beta$  of those variables obtained from logistic regression were used to develop the final 3 stage scores to predict CSA-AKI. The 1152 patients in the validation cohort were scored for validation, and the area under the receiver operating characteristic curves (AUROC) as well as Hosmer-Lemeshow goodness-of-fit test were applied to estimate the reliability of the scoring for predicting CSA-AKI.

## Results

The derivation cohort consisted of 6081 patients, and the validation cohort consisted of 1152 patients. The

**Table 1.** Clinical Characteristics of Derivation and Validation Cohort

	Derivation Cohort (N=6081)	Validation Cohort (N=1152)
<b>Preoperative</b>		
Male	3767 (61.9%)	725 (62.9%)
Age, y	58 (48, 65)	60 (52, 66)
<b>Renal function</b>		
Serum creatinine, $\mu\text{mol/L}$	77 (65, 89)	78 (66, 90)
eGFR, mL/min per 1.73 m <sup>2</sup>	88.7 (69.7, 99.6)	86.5 (67.6, 101.6)
<b>Comorbidities</b>		
Hypertension	2012 (33.1%)	403 (34.9%)
DM	763 (12.5%)	200 (17.4%)
COPD	43 (0.7%)	9 (0.8%)
CVD	83 (1.4%)	14 (1.2%)
Kidney disease without RRT	217 (3.6%)	11 (1.0%)
<b>Heart function</b>		
NYHA classification >2	3428 (56.4%)	648 (56.2%)
NYHA classification $\leq$ 2	2653 (43.6%)	504 (43.7%)
LVEF >50%	5030 (82.7%)	978 (84.9%)
35 < LVEF $\leq$ 50	968 (15.9%)	157 (13.6%)
LVEF $\leq$ 35%	83 (1.3%)	17 (1.5%)
Previous cardiac surgery	84 (1.4%)	25 (2.2%)
CM exposure	2464 (40.5%)	395 (34.3%)
<b>Intraoperative</b>		
Emergency	11 (0.2%)	3 (0.3%)
<b>Procedure</b>		
Valve	3975 (65.4%)	794 (68.9%)
CABG	1527 (25.1%)	325 (28.2%)
OPCAB	286 (4.7%)	45 (3.9%)
Valve and CABG	293 (4.8%)	47 (4.1%)
CPB	4083 (67.1%)	792 (68.8)
Erythrocyte transfusion, U	1 (0, 2)	1 (0, 2)
<b>Postoperative</b>		
LCOS	158 (2.6%)	35 (3.1%)
CVP, cm H <sub>2</sub> O	9 (7, 11)	10 (8, 10)
<b>Prognosis</b>		
28-day mortality	170 (2.8%)	39 (3.4%)

AKI indicates acute kidney injury; CABG, coronary artery bypass grafting; CM, contrast media; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVD, cerebral vascular disease; CVP, central venous pressure by ICU admittance; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate, as was calculated based on the CKD-EPI formulas; LCOS, low cardiac output syndrome; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OPCAB, off-pump coronary artery bypass.

characteristics of both cohorts were showed in Table 1. The incidence of CSA-AKI and mortality in the derivation cohort were 35.5% (2159/6081) and 2.8% (170/6081), whereas in the validation cohort they were 33.0% (380/1152) and 3.4% (39/1152).

### Risk Factor Analysis

The perioperative characteristics of the derivation cohort are presented in Table 2. We categorized the following variables for subgroup observation: age ( $\leq$ 40, 41–60, 61–80,  $\geq$ 81), estimated GFR ( $>$ 60,  $>$ 30 to  $\leq$ 60,  $\leq$ 30 mL/min), and LVEF ( $>$ 50, 36–50,  $\leq$ 35). There were statistically significant differences between the CSA-AKI patients and the unaffected group regarding sex, age, preoperative kidney function, some comorbidities such as hypertension and COPD, preoperative heart function, CM exposure, procedure type, perioperative erythrocyte transfusion, postoperative central venous pressure, and short-term mortality (Table 2). All these risk factors were brought into a multivariate analysis for predicting CSA-AKI. The multivariate logistic regression analysis was conducted at 3 time points: preoperative, ICU admittance, and 24 hours after ICU admittance; the statistically significant risk factors identified by the analysis are shown in Table 3, which shows that male sex, age, kidney disease without RRT, NYHA score  $>$ 2, previous cardiac surgery, valve and CABG procedure, application of CPB, erythrocyte transfusion, and postoperative LCOS at the indicated time points were risk factors for CSA-AKI development (Table 3).

### Score Development

Next we developed a point system for predicting CSA-AKI occurrence with the regression coefficient data from the multivariable regression analyses of the derivative cohort patients (Table 4). Depending on the scores, the risks of CSA-AKI development were categorized into low, medium, and high in accordance with the practically observed incidence of CSA-AKI (Table 5). The preoperative predictive risks of CSA-AKI occurrence were low with 0 to 1 patient (9.5%), medium with 2 to 3 patients (22.1%), and high with  $\geq$ 4 patients (37.3%). The predictive risks of CSA-AKI development at the day of ICU admission were low with 0 to 4 patients (11.5%), medium with 5 to 9 patients (42.6%), and high with  $\geq$ 10 patients (83.3%). The postoperative predictive risks for developing CSA-AKI were low with 0 to 4 patients (11.6%), medium with 5 to 9 patients (44.2%), and high with  $\geq$ 10 patients (88.8%). The efficiency of the scores for predicting medium and high risk for CSA-AKI improved with the procedure progress and additional risk factors being added. We further analyzed the score models at the 3 time

**Table 2.** Characteristics of the Patients in the Derivation Cohort

	Entire Cohort (N=6081)	No AKI (N=3922)	AKI (N=2159)	P Value
<b>Preoperative</b>				
Male	3767 (61.9%)	2254 (57.5%)	1513 (70.1%)	<0.01
Age, y	58 (48, 65)	57 (46, 65)	60 (52, 67)	<0.01
<b>Kidney function</b>				
Serum creatinine, $\mu\text{mol/L}$	77 (65, 89)	73 (63, 86)	81 (70, 97)	<0.01
eGFR, mL/min per 1.73 m <sup>2</sup>	88.7 (72.3, 101.9)	92.0 (76.7, 104.6)	81.7(65.5, 96.3)	<0.01
>60 mL/min	5373 (88.3%)	3635 (92.7%)	1738 (80.5%)	<0.01
30 < eGFR $\leq$ 60 mL/min	659 (10.8%)	273 (6.9%)	386 (17.9%)	<0.01
$\leq$ 30 mL/min	49 (0.9%)	14 (0.4%)	35 (1.6%)	<0.01
<b>Comorbidities</b>				
Hypertension	2012 (33.1%)	1164 (29.7%)	848 (39.3%)	<0.01
DM	763 (12.5%)	471 (12.0%)	292 (13.5%)	0.09
COPD	43 (0.7%)	2 (0.1%)	41 (1.9%)	<0.01
CVD	83 (1.4%)	15 (0.4%)	68 (3.1%)	<0.01
Kidney disease without RRT	217 (3.6%)	90 (2.3%)	127 (5.9%)	<0.01
<b>Cardiac function</b>				
NYHA classification >2	3428 (56.4%)	2075 (52.9%)	1353 (62.7%)	<0.01
NYHA classification $\leq$ 2	2653 (43.6%)	1847 (47.1%)	806 (37.3%)	<0.01
LVEF >50%	5030 (82.7%)	3412 (87.0%)	1618 (74.9%)	<0.01
35 < LVEF $\leq$ 50	968 (15.9%)	482 (12.3%)	486 (22.5%)	<0.01
LVEF $\leq$ 35%	83 (1.3%)	28 (0.7%)	55 (2.5%)	<0.01
Previous cardiac surgery	84 (1.4%)	42 (1.2%)	42 (1.9%)	0.008
CM exposure	2464 (40.5%)	1600 (40.8%)	864 (40.0%)	0.567
<b>Intraoperative</b>				
Emergency	11 (0.2%)	8 (0.2%)	3 (0.2%)	0.06
<b>Procedure</b>				
Valve	3975 (65.4%)	2642 (67.4%)	1333 (61.7%)	<0.01
CABG	1527 (25.1%)	1109 (28.3%)	418 (19.4%)	<0.01
OPCAB	286 (4.7%)	23 (0.6%)	263 (12.2%)	<0.01
Valve and CABG	293 (4.8%)	148 (3.8%)	145 (6.7%)	<0.01
CPB	4083 (67.1%)	2550 (65.0%)	1533 (71.0%)	<0.01
Erythrocyte transfusion, U	1 (0, 2)	1 (0, 2)	1 (0, 2)	<0.01
<b>Postoperative</b>				
LCOS	158 (2.6%)	19 (0.5%)	139 (6.4%)	<0.01
CVP, cm H <sub>2</sub> O	9 (7, 11)	8 (6, 11)	10 (8, 12)	<0.01
<b>Prognosis</b>				
28-day mortality	170 (2.8%)	31 (0.8%)	139 (6.4%)	<0.01

AKI indicates acute kidney injury; CABG, coronary artery bypass grafting; CM, contrast media; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVD, cerebral vascular disease; CVP, central venous pressure by ICU admittance; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate, as was calculated based on the CKD-EPI formulas; LCOS, low cardiac output syndrome; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OPCAB, off-pump coronary artery bypass.

points by AUROC determinations and derived 0.75 (preoperative), 0.81 (ICU admittance), and 0.82 (24 hours after ICU admittance) area under curve (AUC) values. The calibrations

of them by Hosmer-Lemeshow statistics resulted in 0.569 (preoperative), 0.684 (ICU admittance), 0.829 (24 hours after ICU admittance).

**Table 3.** Multivariate Logistic Regression Analysis of Factors for CSA-AKI\*

Variables	$\beta$	P Value	OR	95% CI	
<b>Preoperative</b>					
Male	0.533	<0.01	1.704	1.516	1.914
Age, y <sup>†</sup>					
41 to 60	0.747	<0.01	2.110	1.622	2.745
61 to 80	0.884	<0.01	2.422	1.862	3.149
≥81	0.947	0.013	2.579	1.221	5.449
Kidney disease (without RRT)	0.754	<0.01	1.932	1.692	3.105
NYHA classification >2	0.364	<0.01	1.487	1.304	1.665
Previous cardiac surgery	0.388	0.011	1.475	1.093	1.990
<b>ICU admittance</b>					
Male	0.677	<0.01	2.032	1.698	1.876
Age, y <sup>†</sup>					
41 to 60	0.877	<0.01	2.405	1.816	3.184
61 to 80	1.122	<0.01	3.071	2.300	4.099
≥81	1.367	<0.01	3.923	1.666	9.235
Kidney disease (without RRT)	0.936	<0.01	2.076	1.845	2.547
NYHA classification >2	0.332	<0.01	1.347	1.342	1.523
Previous cardiac surgery	0.354	<0.01	1.452	1.187	1.842
Valve and CABG	0.643	<0.01	1.887	1.452	1.872
Erythrocyte transfusion (per unit)	0.652	<0.01	1.652	1.025	1.176
<b>24 hours after ICU admittance</b>					
Male	0.651	<0.01	1.918	1.639	2.244
Age, y <sup>†</sup>					
41 to 60	0.868	<0.01	2.382	1.788	3.173
61 to 80	1.173	<0.01	3.233	2.397	4.358
≥81	1.315	<0.01	3.726	1.565	8.875
Kidney disease (without RRT)	1.029	<0.01	2.799	2.001	3.914
CPB application	0.489	<0.01	1.631	1.39	1.914
Previous cardiac surgery	0.468	<0.01	1.596	1.309	1.946
Valve and CABG	0.626	<0.01	1.833	1.579	2.232
Erythrocyte transfusion (per unit)	0.856	<0.01	2.376	1.588	2.365
LCOS	1.387	<0.01	3.542	2.234	4.763

CABG indicates coronary artery bypass grafting; CSA-AKI, cardiac surgery associated acute kidney injury; LCOS, low cardiac output syndrome; NYHA, New York Heart Association; RRT, renal replacement therapy.

\*Only the statistically significant risk factors in the logistic regression were contained in this table.

†The variable age was categorized and (age ≤40) was set as the reference level.

### Score Validation

The clinical characteristics of the 1152 patients in the validation cohort are shown in Table 1. Application of the scoring system led to AUC values of 0.74 (preoperative), 0.75 (at ICU admission), and 0.82 (postoperative) (Figure 1). The calibration of the scores is shown in Figure 2. There was no statistically significant difference between the predicted and observed CSA-AKI incidences in the validation cohort

(preoperative  $\chi^2=6.346$ ,  $P=0.175$ ; at the day of ICU admittance  $\chi^2=4.65$ ,  $P=0.703$ ; and postoperative  $\chi^2=3.669$ ,  $P=0.886$ ).

### Discussion

In our study we utilized the KDIGO definition of AKI to establish the dynamic risk score to predict CSA-AKI. With the

**Table 4.** Factor Scoring for Predicting of CSA-AKI Development

Variables	Points
<b>Preoperative</b>	
Male	1
Age, y	
≤40	0
41 to 60	1
61 to 80	2
≥81	3
Kidney disease (without RRT)	1
NYHA classification >2	1
Previous cardiac surgery	1
<b>ICU admittance</b>	
Male	1
Age, y	
≤40	0
41 to 60	1
61 to 80	2
≥81	3
Kidney disease (without RRT)	1
NYHA classification >2	1
Previous cardiac surgery	1
Valve and CABG	1
Erythrocyte transfusion	1/unit
<b>24 hours after ICU admittance</b>	
Male	1
Age, y	
≤40	0
41 to 60	1
61 to 80	2
≥81	3
Kidney disease (without RRT)	1
CPB application	1
Previous cardiac surgery	1
Valve and CABG	1
Erythrocyte transfusion (per unit)	1/unit
LCOS	1

CABG indicates coronary artery bypass grafting; CPB, cardiopulmonary bypass; CSA-AKI, cardiac surgery associated acute kidney injury; ICU, intensive care unit; LCOS, low cardiac output syndrome; NYHA, New York Heart Association.

KDIGO guideline, which is accepted by the global nephrology community, some authors carried out risk factor analysis for CSA-AKI<sup>16,17</sup> with the new AKI definition. To the best of our knowledge, there were no dynamically designed risk scores

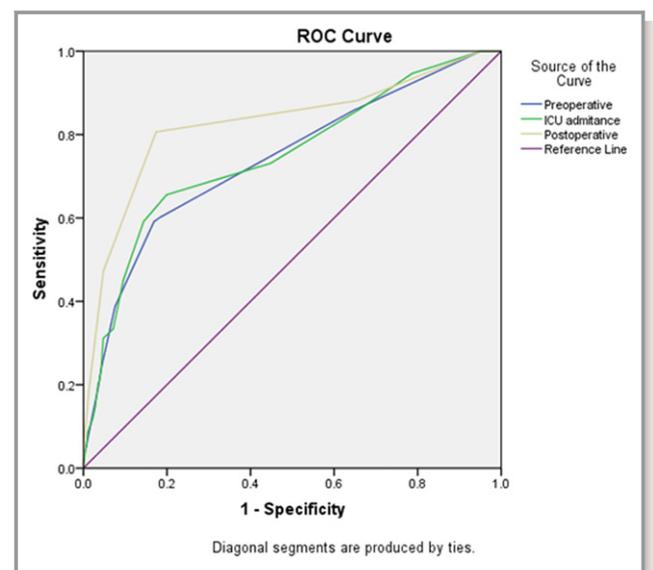
**Table 5.** Risk Stratification of CSA-AKI Development at Indicated Time Points

Sum Points	Preoperative	ICU Admittance	24 Hours After ICU Admittance
0 to 1 pts	Low	Low	Low
2 to 3 pts	Medium	Low	Low
4 pts	High	Low	Low
5 to 9 pts	High	Medium	Medium
≥10 pts	High	High	High

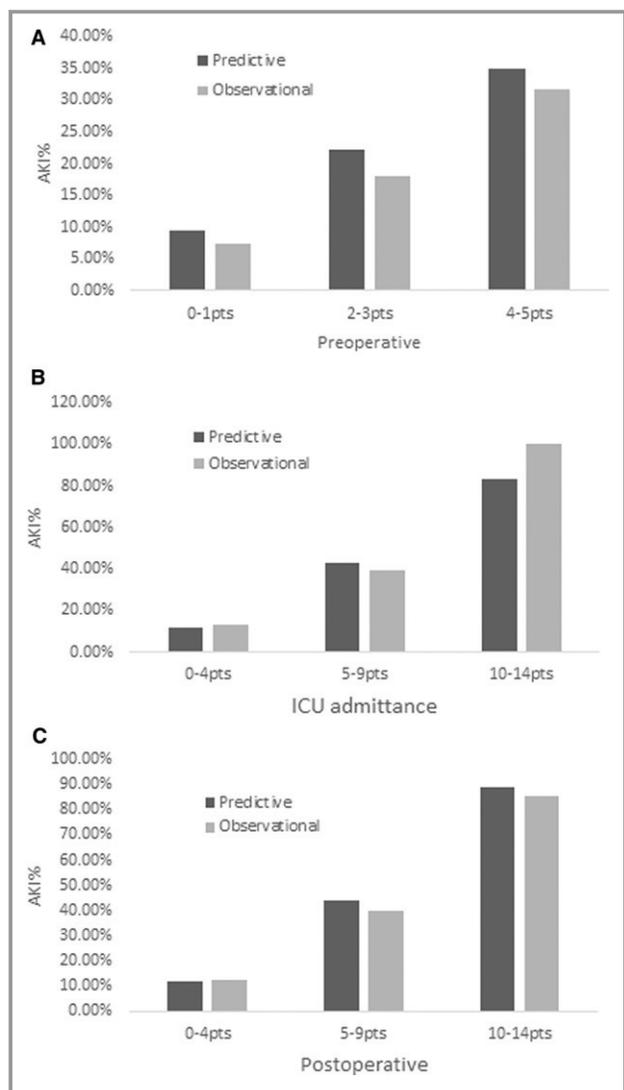
The distinction of low/medium/high was based on the incidence of CSA-AKI in each sector; eg, the incidence of AKI in the sector of ≥10 pts in the 24 hours after ICU admittance column was 88.8%, which meant in the patients who scored ≥10 points at the time of 24 hours after admission, the incidence of CSA-AKI was 88.8%. CSA-AKI indicates cardiac surgery-associated acute kidney injury.

for predicting CSA-AKI from preoperative to early postoperative periods. Not only pre-op risk factors but also the intra-op and post-op risk factors were enrolled in the analysis for better predictive efficiency. The result of our study showed that the predictive value of the dynamic risk scores was close to that of the previous scores and improved as the intra-op (AUC=0.75) and post-op (AUC=0.82) risk factors were admitted into the multivariate regression analysis and the subsequent scores. These risk scores can help clinicians to evaluate the risk of CSA-AKI from preoperative to early postoperative periods.

In this study all the major risk factors of CSA-AKI were collected to derive the predictive score system, including the intra-op and post-op risk factors.

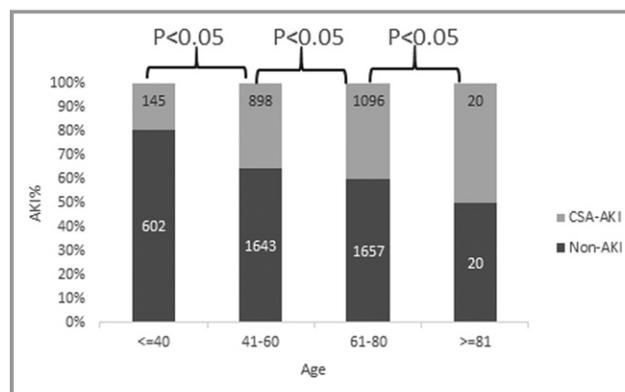


**Figure 1.** ROC curves for predicting CSA-AKI in the validation cohort with point scores from Table 5. \*Application of the scoring system led to AUC values of 0.74 (preoperative), 0.75 (at ICU admission), and 0.82 (postoperative).



**Figure 2.** Score calibrations for predicting CSA-AKI (A) preoperative, (B) at the day of ICU admittance, (C) postoperative. \*There was no statistically significant difference between the CSA-AKI incidences predicted by point scores and those observed in the validation cohort (preoperative  $\chi^2=6.346$ ,  $P=0.175$ ; at the day of ICU admittance  $\chi^2=4.65$ ,  $P=0.703$ ; and postoperative  $\chi^2=3.669$ ,  $P=0.886$ ). CSA-AKI indicates cardiac surgery–associated acute kidney injury.

Male sex and age were risk factors for CSA-AKI in all 3 time points, and with increasing age, the incidence of CSA-AKI also increased. Age-associated AKI was reported to occur more frequently in the elderly due to structural changes such as vascular sclerosis, increased percentages of sclerosing glomeruli, and other degenerative changes that occur with increasing age,<sup>18,19</sup> and our finding is in agreement with other publications from Fang et al,<sup>20,21</sup> who noted that the incidence of CSA-AKI in the older patients was higher than that in younger patients. In our cohort we conducted a subgroup analysis according to the categorized age and found



**Figure 3.** Subgroup analysis between categorized age groups for CSA-AKI incidence. \*The CSA-AKI incidence was statistically significantly different within the subgroups, and increased with age. CSA-AKI indicates cardiac surgery–associated acute kidney injury.

significant differences in CSA-AKI incidence between groups (Figure 3). The risk factor of male sex is in disagreement with other publications in which female sex was a risk factor,<sup>22,23</sup> which needs further analysis.

Another CSA-AKI risk factor was preoperative kidney disease without renal replacement therapy. Preoperative renal dysfunction was related to CSA-AKI in several other studies.<sup>4,8,23</sup> However, we excluded preoperative RRT patients and also drew the same conclusion. In Table 2, the eGFR was statistically significantly different between AKI and non-AKI cohorts ( $P<0.01$ ). In the subsequent subgroup analysis, we found significant differences in the incidence of CSA-AKI among subgroups. However, unlike age, categorized eGFR were eliminated through logistic regression. The possible reason may be that we brought many more parameters, such as “previous kidney disease without RRT,” into our study in order to improve prediction, so the relationship between eGFR and CSA-AKI could be somehow diluted in the multivariate analysis. Another possible reason was that the kidney function (preoperative serum creatine and eGFR) in our cohorts was better than that of existing model derivation cohorts.

The predictors above were also listed in the previous scores; the innovation and superiority of our scores result from our inclusion of intra-op and post-op predictors. With the awareness of intra-op and post-op risk factors contributing to CSA-AKI, the risk stratification based on only pre-op risk factors does not take into account the patients’ physiological response to the surgeon and post-op treatment as well as the occurrence of adverse events in the intra-op and post-op periods, which increase the risk of CSA-AKI. Patients undergoing cardiac surgery typically exhibit complex syndromes with numerous pathways that affect renal function and involve hemodynamic changes, tissue breakdown, reactive oxygen species, infection, and drug toxicity. All of these factors can

result in endothelial dysfunction, blood dynamics disorders, inflammatory responses, and tubular cell damage.

Intraoperative erythrocyte transfusion was recognized as predictor for CSA-AKI in our study. Previous studies also found a correlation of erythrocyte transfusion and CSA-AKI,<sup>24,25</sup> and it has been reported that the posttransfusion recovery of red blood cells is lower after long-term storage<sup>26</sup>; the morphological and biochemical changes during storage have been suggested to promote a proinflammatory state, impair tissue oxygen delivery, and exacerbate tissue oxidative stress due to free iron, which in turn is an AKI risk factor for susceptible CPB patients.<sup>27</sup> Some studies suggest that each unit of perioperative blood transfusion is significantly associated with a 10% to 20% increase in the risk of AKI after cardiac surgery with CPB<sup>25,28</sup> in spite of the different AKI definitions. Some surgical teams trying to reduce the potential renal harm of erythrocyte transfusion have found promising options,<sup>29</sup> including reducing perioperative hemodilution by minimizing fluid administration and retrograde autologous priming of the cardiopulmonary circuit, salvage of shed blood, tolerance of moderate hemodilution, and early identification and treatment with erythropoietin-stimulating agents and iron therapy.

In previous studies some complex procedures, especially valve surgery combined with CABG, were found to increase the incidence of CSA-AKI.<sup>6–9</sup> This conclusion was also proven in our study, in which valve combined with CABG was one of the risk factors. Perioperative cardiac function has a definite impact on CSA-AKI. Chetow et al<sup>4</sup> found local renal ischemia injury due to insufficient perfusion contributes to CSA-AKI. Preoperative NYHA scores >2, previous cardiac surgery, and postoperative LCOS were also found to be risk factors for CSA-AKI in our study. Among the above factors, preoperative

NYHA scores >2 and previous cardiac surgery are not modifiable. The LCOS may result from delayed recovery of post-op cardiac function and cause pulmonary edema and pulmonary infection, which in turn aggravate LCOS in a vicious circle.<sup>30</sup> For those CSA-AKI patients who were unable to eliminate excess fluid and adverse inflammatory factors, either LCOS or pulmonary infection would result in a worse prognosis. Some studies<sup>31</sup> were carried out to break this vicious circle by means of “perioperative goal-directed hemodynamic resuscitation therapy,” which was considered to be useful in reducing adverse complications including LCOS as well as 30-day mortality in high-risk patients undergoing cardiac surgery.

AKI is one of the common complications after cardiac surgery. The lack of a consensus AKI definition has led to inaccuracy in data regarding the actual incidence of this complication, as can be confirmed by the large variation (1% to 30%) in the reported incidence of AKI following cardiac surgery.<sup>22</sup> By the time of this study, no consensus AKI definition was utilized in the risk scores above, and so their worldwide applicability is suspect. The KDIGO criterion, published in 2012, was regarded as a complement to previous AKI definitions.<sup>32,33</sup> Sampaio et al compared the KDIGO AKI definition with AKIN and RIFLE criteria and validated its superiority, especially for prognoses in unstable hemodynamic cardiac surgery patients.<sup>34</sup> Therefore, risk scores with the KDIGO AKI definition were better for predicting CSA-AKI.

Cardiac surgery in developing countries such as China, India, and Brazil has grown at a steady pace for decades, but most centers performing open heart surgery are located in the major cities, which is a common problem for most developing countries. Although as the economy has developed, and

**Table 6.** Comparison of Derivation Cohort and Other Risk Scores in Comorbidities and Procedures

	Derivation Cohort (n=6081)	AKICS (n=603)	Cleveland (n=15 838)	Mehta (n=449 524)	SRI (n=10 751)
<b>Comorbidities</b>					
Hypertension	2012 (33.1%)	500 (82.6%)	—	75.2%	5891 (54.8%)
DM	763 (12.5%)	169 (28%)	3857 (24.3%)	33.2%	2381 (22.1%)
COPD	43 (0.7%)	—	1326 (8.4%)	19.6%	427 (3.9%)
CVD	83 (1.4%)	28 (4.6%)	2713 (17.1%)	13.8%	968 (9%)
Kidney disease without RRT	217 (3.6%)	—	—	—	—
<b>Procedure</b>					
Valve	3975 (65.4%)	794 (37%)	4086 (25.8%)	10.3%	1755 (16.3%)
CABG*	1813 (29.8%)	319 (53%)	8314 (52.5%)	78.6%	7005 (65.1%)
Valve and CABG	293 (4.8%)	61 (10%)	2594 (16.4%)	10.1%	1991 (18.5%)

CABG indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVD, cerebral vascular disease; DM, diabetes mellitus; RRT, renal replacement therapy; SRI, simplified renal index.

\*Including off-pump coronary artery bypass.

cardiac surgery has become affordable for more patients, its complications are adding to the social economic burden in developing countries.<sup>35,36</sup> Considering the tremendous population in developing countries, this is worthy of concern.

The occurrence of valve surgery is becoming higher in developing countries such as China than it was in previous risk stratification development centers, in which CABG is the major procedure (Table 6). This change may be due to the lack in early diagnosis and imbalanced distribution of medical resources; it is also one of the reasons why CSA-AKI incidence was high in our cohort. Compared to CABG, the pathophysiology and pathological impairment are diversified. Patients who undergo valve surgery typically demonstrate low stroke volume related to regurgitation, which increases the vulnerability of the kidney to injury during cardiac surgery. The comorbidities in developing countries such as China are also different from those in the Western population. In our derivation cohort, the ratios of hypertension and diabetes mellitus are also remarkably lower than those in the previous developmental populations (Table 6).

Therefore, the difference in ethnicity, comorbidities, and underlying disease may affect the efficacy of the existing models predicting CSA-AKI in patients of developing countries.

As in Thakar's and Palomba's studies,<sup>7,8</sup> the present risk scores are validated in a sample extracted from the original population with good discrimination and calibration. For simpler clinical application, the scores are stratified in categories according to the predictive risk of CSA-AKI. The maximum predictive risk of 88.8%, which is higher than those in other studies, may be attributed to the KDIGO AKI definition, which was verified with better efficacy, and the inclusion of intra-op and post-op predictors, with which the course of disease can be well simulated.

The limitation of this study was that the data were derived from a single-center Chinese database, implying differences in procedures and comorbidities with other existing risk scores, so their predictive efficiency should be prospectively validated in more centers and on a larger scale.

## Conclusion

We carried out this study prospectively and developed dynamic predictive scores for CSA-AKI in cardiac surgical patients with the KDIGO definition for AKI. This may improve the early recognition and intervention against CSA-AKI, fix those modifiable factors, reduce the incidence of CSA-AKI, and improve the renal and overall prognosis. Embedding these scores into the electronic medical record (EMR) system may improve their clinical practical utility.

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## Disclosures

None.

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