Original Paper

Clinical Prediction Scores for Type 1 Cardiorenal Syndrome Derived and Validated in Chinese Cohorts

Hong Cheng Yi-pu Chen

Division of Nephrology, Beijing Anzhen Hospital, Capital Medical University,
Beijing, PR China**Key Words**

Prediction score · Cardiorenal syndrome · Acute kidney injury

Abstract

Type 1 cardiorenal syndrome is one of the major diseases threatening human life in China. The incidence of acute kidney injury (AKI) associated with acute heart failure (AHF), acute myocardial infarction (AMI), cardiac surgery, and coronary angiography has been reported to be 32.2, 14.7, 40.2, and 4.5%, respectively. In the past 2 years, we derived and validated 4 risk scores for the prediction of AKI associated with the above acute heart diseases as well as for examination and treatment in Chinese cohorts. A univariable comparison and a subsequent multivariate logistic regression analysis of the potential predictive variables of AKI in the derivation set were conducted and used to establish the prediction scores, which were then verified in the validation set. The area under the receiver operating characteristic (ROC) curve and the Hosmer-Lemeshow goodness-of-fit statistic test were performed to assess the discrimination and calibration of the prediction scores, respectively. These 4 prediction scores all showed adequate discrimination (area under the ROC curve, ≥ 0.70) and good calibration ($p > 0.05$). Both Forman's risk score (for AKI associated with AHF) and Mehran's risk score (for AKI associated with coronary angiography) are widely applied around the world. The external validation of these 2 risk scores was performed in our patients, but their discriminative power was quite low (area under the ROC curve, 0.65 and 0.57, respectively). Therefore, these prediction scores derived from Chinese cohorts might be more accurate than those derived from different races when they are applied in Chinese patients.

© 2014 S. Karger AG, Basel

Yi-pu Chen
Division of Nephrology, Beijing Anzhen Hospital
Capital Medical University
Beijing 100029 (PR China)
E-Mail chen_yipu@medmail.com.cn

Need to Develop Prediction Scores for Type 1 Cardiorenal Syndrome in Chinese Patients

In 2008, the first international consensus conference on cardiorenal syndrome (CRS) was held in Venice, Italy, under the auspices of the Acute Dialysis Quality Initiative [1]. At the conference, CRS was classified into 5 types. Type 1 is defined as acute CRS, characterized by an acute worsening of the heart function leading to acute kidney injury (AKI). The primary events in type 1 CRS include acute heart failure (AHF), acute coronary syndrome, and cardiogenic shock [1]. Broadly speaking, the primary events also include heart disease-related medical procedures, such as cardiac surgery and coronary angiography [2].

With an aging population, the prevalence of cardiovascular disease is continuously increasing, and it has become one of the major diseases threatening human life in China. Type 1 CRS is commonly encountered in clinical practice. Retrospective analyses of the data of the hospitalized patients in our hospital, the Beijing Anzhen Hospital, Capital Medical University, showed that the AKI incidence in the patients with AHF ($n = 550/1,709$), acute myocardial infarction (AMI) ($n = 210/1,429$), cardiac surgery ($n = 1,407/3,500$), or coronary angiography ($n = 177/3,945$) was 32.2, 14.7, 40.2, and 4.5%, respectively [3–6]. The patients with type 1 CRS had poorer in-hospital outcomes, including higher all-cause mortality, compared with the patients without type 1 CRS (table 1). Therefore, once AKI occurs, the death risk of patients with acute heart diseases obviously is increased.

The Anzhen Hospital is one of the largest cardiovascular centers in China, and, to a certain extent, our epidemiological data might be expected to reflect the current situation at most large hospitals in China. Therefore, how to prevent type 1 CRS is an urgent problem waiting to be solved.

In the past decade, several clinical risk scores for predicting the occurrence of AKI in patients with AHF [7, 8] or AMI [9] as well as in patients after cardiac surgery [10–14] or coronary angiography [15–20] were published. The application of these prediction scores in clinical practice has shown great benefits in the prevention of type 1 CRS. However, so far, no such prediction score has been derived from the data of Chinese patients. Since a prediction score may be more accurate for the population from whom it was derived, it is necessary to develop risk scores for predicting type 1 CRS in the Chinese population [6].

Method and Process for Creating Risk Scores of Type 1 CRS

In the past 2 years, we derived and validated 4 risk scores for the prediction of AKI associated with acute heart diseases and related medical procedures using the abundant resources of patients with heart diseases in our hospital. The patients enrolled in these studies were

Table 1. Mortality of patients studied

	With type 1 CRS	Without type 1 CRS	p value
AHF	16.5%	1.9%	<0.01
AMI	9.0%	0.5%	<0.01
Cardiac surgery	5.2%*	0.5%	<0.01
Coronary angiography	3.4%	0.3%	<0.01

* The mortality of the patients requiring dialysis was 50.7%.

Table 2. Prediction score for AKI in patients with AHF

Risk factors	Score
Age ≥ 70 years	3
SBP < 90 mm Hg	4
Serum sodium < 130 mmol/l	2
Heart function class IV	2
≥ 3 admissions for AHF	3
Proteinuria	2
Serum creatinine*	
104–176 $\mu\text{mol/l}$	5
177–264 $\mu\text{mol/l}$	7
≥ 265 $\mu\text{mol/l}$	10
Intravenous furosemide	
80–159 mg/day	3
≥ 160 mg/day	5

SBP = Systolic blood pressure.

* The upper limit of the normal serum creatinine concentration in our hospital is 103 $\mu\text{mol/l}$.

randomly divided into a derivation group (60–70% of patients) and a validation group (30–40% of patients). The potential predictor variables were selected based on our clinical experience and literature review. In the validation group, a univariate comparison of the potential predictor variables between AKI and non-AKI patients was performed, and the likely predictor variables obtained from this analysis were then included in a multivariate logistic regression model. The independent predictors of AKI identified in the multivariate model were then assigned weighted integer values based upon their odds ratios or beta coefficients. All 4 prediction scores were created in this way. The discrimination of the prediction scores was quantified using the area under the receiver operating characteristic (ROC) curve. The calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test and considered satisfactory when the p value was > 0.05 . Finally, the validation of the prediction score was implemented in the validation dataset [3–6].

The 4 Risk Scores for the Prediction of Type 1 CRS in Chinese Patients

The Prediction Score for AKI in Patients with AHF

A prediction score for AKI in the hospitalized AHF patients was developed based on the data analysis of a total of 1,709 cases (950 males, 759 females; table 2) [3]. AHF and AKI were diagnosed according to the 2012 guidelines of the European Society of Cardiology (ESC) [21] and the 2007 criteria of the Acute Kidney Injury Network (AKIN) [22], respectively. Based on the prediction score, the incidence of AKI in the very-low-risk group (cumulative score 0–3), low-risk group (4–7), moderate-risk group (8–11), high-risk (12–15), and very-high-risk group (≥ 16) was 13.5, 22, 43.3, 66.1, and 82.4%, respectively. In both the derivation and validation datasets, the prediction score showed adequate discrimination (area under the ROC curve, 0.76 in both datasets) and good calibration (Hosmer-Lemeshow statistical test, $p = 0.98$ and $p = 0.13$, respectively) [3].

Forman's risk score [7] has been widely applied worldwide. In the present study, we conducted an external validation of Forman's risk score by using the same 1,709 patients, which showed that the area under the ROC curve was only 0.65 [3]. By using the test proposed

Table 3. Prediction score for AKI in patients with AMI

Risk factors	Score
Killip class $\geq$ III at admission	3
Shock	3
Interval from AMI onset to admission $\geq$ 6 h	2
Extensive anterior myocardial infarction	1
Hypertension	1
Nonuse of β -blocker	1
eGFR	
80.0–89.9 ml/min/1.73 m ²	1
70.0–79.9 ml/min/1.73 m ²	2
60.0–69.9 ml/min/1.73 m ²	3
50.0–59.9 ml/min/1.73 m ²	4
40.0–49.9 ml/min/1.73 m ²	5
30.0–39.9 ml/min/1.73 m ²	6
<30 ml/min/1.73 m ²	7
eGFR = Estimated glomerular filtration rate.	

by DeLong et al. [23], our prediction score improved by 0.11 in the area under the ROC curve compared with Forman's risk score [3].

The Prediction Score for AKI in Patients with AMI

A prediction score for AKI in the patients with AMI was also established on the basis of the data analysis of a total of 1,429 cases (1,138 males, 291 females; table 3) [4]. AMI was confirmed according to the 2007 universal definition of myocardial infarction proposed by the ESC, the American College of Cardiology (ACC), the American Heart Association (AHA), and the World Heart Federation (WHF) [24]. AKI was diagnosed in accordance with the 2007 criteria of the AKIN [22]. Based on this prediction score, the incidence of AKI in the low-risk group (cumulative score 0–3), moderate-risk group (4–6), and high-risk group ($\geq$ 6) was 5.0, 14.7, and 41.3%, respectively. In both the derivation and validation datasets, the prediction score also showed adequate discrimination (area under the ROC curve, 0.77 and 0.70, respectively) and good calibration (Hosmer-Lemeshow statistical test, $p = 0.53$ and $p = 0.13$, respectively) [4].

The Prediction Score for AKI after Cardiac Surgery

A prediction score for AKI in the patients who had undergone cardiac surgery was also created based on the data of a total of 3,500 cases (2,263 males, 1,237 females; table 4). AKI was defined as an increase in the serum creatinine level of ≥ 0.3 mg/dl (≥ 26.4 μ mol/l) or $\geq 50\%$ (1.5-fold from baseline) and at the same time beyond the upper limit of its normal value within 48 h. Based on this prediction score, the higher the cumulative score, the larger the risk of AKI (table 5). In both the derivation and validation datasets, the prediction score also showed adequate discrimination (area under the ROC curve, 0.75 and 0.74, respectively) and good calibration (Hosmer-Lemeshow statistical test, $p = 0.55$ and $p = 0.31$, respectively) [5].

The Prediction Score for Contrast-Induced Nephropathy after Coronary Angiography

A prediction score for AKI in patients who had undergone coronary angiography was also developed based on the data analysis of a total of 3,945 cases (2,781 males, 1,164 females; table 6) [6]. Contrast-induced nephropathy (CIN) was defined as an increase in the serum

Table 4. Prediction score for AKI in patients who underwent cardiac surgery

Risk factors	Score
Male gender	2
Age	
61–65 years	1
66–70 years	2
71–75 years	3
76–80 years	4
≥81 years	5
Diabetes mellitus	2
Preoperative use of ACEI/ARB	1
Preoperative eGFR	
80–89.9 ml/min/1.73 m ²	1
70–79.9 ml/min/1.73 m ²	2
60–69.9 ml/min/1.73 m ²	3
50–59.9 ml/min/1.73 m ²	4
40–49.9 ml/min/1.73 m ²	5
30–39.9 ml/min/1.73 m ²	6
≤29.9 ml/min/1.73 m ²	7
NYHA class IV	3
CPB time >120 min	2
Intraoperative hypotension for >60 min	2
Postoperative hypotension for >60 min	3
Postoperative use of furosemide	
60–100 mg/day	2
>100 mg/day	3
Postoperative mechanical ventilation for 1 h	2

ACEI = Angiotensin-converting enzyme inhibitors; ARB = angiotensin AT1 receptor blockers; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association; CPB = cardiopulmonary bypass.

Table 5. Risk score and AKI incidence

Cumulative score	AKI incidence, %
0–1	8.1
2–3	16.5
4–5	26.3
6–7	37.4
8–9	46.9
10–11	63.2
12–13	77.4
14–15	83.1
≥16	92.3

creatinine level of ≥ 0.5 mg/dl (≥ 44.2 μ mol/l) or $\geq 25\%$ and at the same time beyond the upper limit of its normal value within 72 h following intravascular administration of contrast media [25], which is a modified diagnostic criterion from the CIN definition developed by the European Society of Urogenital Radiology (ESUR) in 1999 [26]. Based on this prediction score, the incidence of CIN in the low-risk group (cumulative score 0–4), moderate-risk group (5–8), high-risk group (9–11), and very-high-risk group (≥ 12) was 1.2, 6.3, 16.8, and 27.3%, respectively. In both the derivation and validation datasets, the prediction score also showed

Table 6. Prediction score for CIN after coronary angiography

Risk factors	Score
Age >60 years	2
Hypertension	2
AMI	2
AHF	2
Use of IABP	4
Baseline eGFR	
89–70 ml/min/1.73 m ²	1
69–50 ml/min/1.73 m ²	2
49–30 ml/min/1.73 m ²	3
<30 ml/min/1.73 m ²	6
Contrast volume	
>100 to ≤300 ml	1
>300 ml	3

eGFR = Estimated glomerular filtration rate; IABP = intra-aortic balloon pump.

adequate discrimination (area under the ROC curve, 0.76 and 0.71, respectively) and good calibration (Hosmer-Lemeshow statistical test, $p = 0.50$ and $p = 0.54$, respectively) [6].

Mehran's risk score [15] is widely used around the world including in China. In the present study, we performed an external validation of Mehran's risk score using the same 3,945 patients and found an area under the ROC curve of only 0.57 [6]. This result is quite similar to the result of the external validation for Mehran's risk score by an Italian study (area under the ROC curve was also 0.57) [27].

Value and Limitations of These Prediction Scores

Our data showed that the incidence of AKI in patients with AHF, AMI, cardiac surgery was 32.2, 14.7, and 40.2%, respectively; these rates are quite similar to those reported in most of the literature. The quite high AKI incidence indicated that it is urgent to prevent type 1 CRS in the heart diseases mentioned above.

However, the CIN incidence in our study was 4.5%, which is lower than in other studies [15, 18–20, 28]. Even when a stricter diagnostic criterion was used, the lower CIN incidence might be related to the improvement of the clinicians' knowledge and the use of various preventive measures in the past years in our hospital. Therefore, it is suggested that there is the possibility to reduce the incidence of type 1 CRS by positive prevention.

The application of these prediction scores will be conducive of the risk stratification of AKI for those patients with acute heart diseases and undergoing related medical procedures and can help clinicians to perform early preventive strategies for high-risk patients in order to reduce type 1 CRS. By this means, it is possible to improve the outcome of patients with heart diseases.

Forman's risk score [7] and Mehran's risk score [15] are widely used around the world and are valuable in the prediction of AKI in patients with AHF or undergoing coronary angiography, respectively. However, their discriminative power in our patients was quite low, as shown in our external validation. The fact further verified this view, i.e. predictive results tend to be more accurate when the risk score is applied to the race and nation from which it is derived. Therefore, it is necessary to develop a risk score in the Chinese population.

The 4 prediction scores described herein have a common drawback, that is, they were only based upon a retrospective analysis of the case data collected from a single cardiovascular center. To compensate for this shortcoming, a multicenter prospective external validation is currently being conducted.

Acknowledgements

We thank our postgraduate students Drs. Y.N. Wang, T. Yue, N. Ye, and Y.M. Gao for their creative contribution to the development of these prediction scores. This research was supported by the following 2 grants: National Science and Technology Ministry (ID: 2011BAI10B06) and Capital Medical Development Research Foundation (ID: 2011-2006-07).

References

- 1 Ronco C, McCullough P, Anker SD, et al: Acute Dialysis Quality Initiative (ADQI) consensus group: Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. *Eur Heart J* 2010; 31:703–711.
- 2 Ronco C, Haapio M, House AA, Anavekar N, Bellomo R: Cardiorenal syndrome. *J Am Coll Cardiol* 2008;52: 1527–1539.
- 3 Wang YN, Cheng H, Yue T, Chen YP: Derivation and validation of a prediction score for acute kidney injury in patients hospitalized with acute heart failure in a Chinese cohort. *Nephrology (Carlton)* 2013;18:489–496.
- 4 Yue T, Wang YN, Cheng H, Chen YP: Risk factors and prediction score of acute kidney injury in patients with acute myocardial infarction. *Chin J Intern Med* 2013;33:377–380.
- 5 Ye N, Zhang Y, Cheng H, Chen YP: Clinical predictive score for acute kidney injury after cardiac surgery in adults. *Chin J Clin Thorac Cardiovasc Surg* 2013;24:396–401.
- 6 Gao YM, Li D, Cheng H, Chen YP: Derivation and validation of a risk score for contrast-induced nephropathy after cardiac catheterization in Chinese patients. *Clin Exp Nephrol* 2014, Epub ahead of print.
- 7 Forman DE, Butler J, Wang Y, et al: Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004;43:61–67.
- 8 Breidthardt T, Socrates T, Noveanu M, et al: Effect and clinical prediction of worsening renal function in acute decompensated heart failure. *Am J Cardiol* 2011;107:730–735.
- 9 Queiroz RE, de Oliveira LS, de Albuquerque CA, et al: Acute kidney injury risk in patients with ST-segment elevation myocardial infarction at presentation to the ED. *Am J Emerg Med* 2012;30:1921–1927.
- 10 Palomba H, de Castro I, Neto ALC, Lage S, Yu L: Acute kidney injury prediction following elective cardiac surgery: AKICS Score. *Kidney Int* 2007;72:624–631.
- 11 Thakar CV, Arrigain S, Worley S, Yared J-P, Paganini EP: A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol* 2005;16:162–168.
- 12 Mehta RH, Grab JD, O'Brien SM, et al: Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. *Circulation* 2006;114:2208–2216.
- 13 Wijeyesundera DN, Karkouti K, Dupuis JY, et al: Derivation and validation of a simplified predictive index for renal replacement therapy after cardiac surgery. *JAMA* 2007;297:1801–1809.
- 14 Harel Z, Chan CT: Predicting and preventing acute kidney injury after cardiac surgery. *Curr Opin Nephrol Hypertens* 2008;17:624–628.
- 15 Mehran R, Aymong ED, Nikolsky E, et al: A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004;44: 1393–1399.
- 16 Bartholomew BA, Harjai KJ, Dukkipati S, et al: Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. *Am J Cardiol* 2004;93:1515–1519.
- 17 Brown JR, DeVries JT, Piper WD, et al: Northern New England Cardiovascular Disease Study Group: Serious renal dysfunction after percutaneous coronary interventions can be predicted. *Am Heart J* 2008;155:260–266.
- 18 Ghani AA, Tohamy KY: Risk score for contrast induced nephropathy following percutaneous coronary intervention. *Saudi J Kidney Dis Transpl* 2009;20:240–245.
- 19 Maioli M, Toso A, Gallopin M, et al: Preprocedural score for risk of contrast-induced nephropathy in elective coronary angiography and intervention. *J Cardiovasc Med (Hagerstown)* 2010;11:444–449.
- 20 Tziakas D, Chalikias G, Stacos D, et al: Development of an easily applicable risk score model for contrast-induced nephropathy prediction after percutaneous coronary intervention: a novel approach tailored to current practice. *Int J Cardiol* 2013;163:46–55.

- 21 McMurray JJ, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines: ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;14:803–869.
- 22 Mehta RL, Kellum JA, Shah SV, et al; Acute Kidney Injury Network: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31.
- 23 DeLong ER, DeLong DM, Clarke-Pearson DL: Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–845.
- 24 Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: Universal definition of myocardial infarction. *J Am Coll Cardiol* 2007;50:2173–2195.
- 25 Li D, Gao YM, Cheng H, Chen YP: Comparative study of diagnosis for contrast-induced nephropathy by ESUR and modified ESUR definitions. *Chin J Pract Intern Med* 2011;31:938–940.
- 26 Morcos SK, Thomsen HS, Webb JA: Contrast-media-induced nephrotoxicity: a consensus report. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). *Eur Radiol* 1999;9:1602–1613.
- 27 Sgura FA, Bertelli L, Monopoli D, et al: Mehran contrast-induced nephropathy risk score predicts short- and long-term clinical outcomes in patients with ST-elevation-myocardial infarction. *Circ Cardiovasc Interv* 2010;3:491–498.
- 28 Bouzas-Mosquera A, Vazquez-Rodriguez JM, Calvino-Santos R, et al: Contrast-induced nephropathy and acute renal failure following emergent cardiac catheterization: incidence, risk factors and prognosis (in Spanish). *Rev Esp Cardiol* 2007;60:1026–1034.