Original Paper

Nomogram Model to Predict Cardiorenal Syndrome Type 1 in Patients with Acute Heart Failure

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Key Words

Cardiorenal syndrome type 1 • Acute heart failure • Nomogram

Abstract

Background/Aims: Cardiorenal syndrome type 1 (CRS1) is a serious clinical condition in patients with acute heart failure (AHF) associated with adverse clinical outcomes. Although several biomarkers for identifying CRS1 have been reported, early and accurate predicting CRS1 still remains a challenge. This study was aimed to develop and validate an individualized predictive nomogram for the risk of CRS1 in patients with AHF. **Methods:** A total of 1235 AHF patients between 2013 and 2018 were included in this study. The patients were randomly classified into training set (n=823) and validation set (n=412). All data of the training set were used to screen the predictors of CRS1 via univariate and multivariate analyses. A nomogram was developed based on these predictors and validated by internal and external validation. The nomogram validation comprised discriminative ability determined by the area under the curve (AUC) of receiver-operating characteristic (ROC) curve and the predictive accuracy by calibration plots. **Results:** The overall incidence of CRS1 was 31.7%. Multivariate logistic regression revealed that age, diabetes, NYHA class, eGFR, hs-CRP and uAGT were independently associated with CRS1. A nomogram developed based on the six variables was with the AUC 0.885 and 0.823 on internal and external validation, respectively. Calibration plots showed that the predicted and actual CRS1 probabilities were fitted well on both internal and external validation. **Conclusion:** The proposed nomogram could predict the individualized risk of CRS1 with good accuracy, high discrimination, and potential clinical applicability in patients with AHF.

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Introduction

Cardiorenal syndrome (CRS) is a well-known common and challenging clinical scenario that exemplifies the interaction between heart and kidney [1]. CRS Type 1 (CRS1) is characterized by worsening of cardiac function [eg, acute heart failure (AHF)], resulting in acute kidney injury (AKI)[2]. Nearly 25-44% of AHF patients would develop CRS1 during their hospitalization, which is closely associated with longer hospitalization, increased risk of readmission, morbidity and mortality, and substantial loss of quality of life [3-7]. The adverse clinical outcomes make the identification of patients at high risk for developing CRS1 very critical. Currently, the diagnosis of CRS1 mainly relies on serum creatinine change and urine output which has been found to be too insensitive and too late to detect CRS1 and make beneficial interventions, leading to poor clinical outcomes [8, 9].

Many recent efforts have been made to identify the clinical variables, such as estimated glomerular filtration rate (eGFR), albumin, urinary neutrophil gelatinase-associated lipocalin (uNGAL) and urinary angiotensinogen (uAGT) for the early diagnosis of CRS1[9-14]. However, their effectiveness for predicting CRS1 is still controversial. Currently, despite widespread recognition of the importance of CRS1, there is still no accurate predictive method to detect CRS1 early enough to initiate timely intervention. A nomogram could provide, in an easily accessible form, accurate risk estimate of a specific clinical outcome for each patient based on significant factors. Recently, nomograms have been proposed in the field of various diseases to aid the clinicians in determining the diagnosis and treatment strategy [15-18]. The present research is intended to determine possible predictors and construct a predictive nomogram model for the estimate of the CRS1 risk, which would be helpful for identifying patients at high risk, and then guide patient counseling and selection of appropriate therapy, in the setting of AHF.

Materials and Methods

Patients

1365 consecutive patients diagnosed with AHF at the Department of Cardiovascular, Civil Aviation General Hospital from January 2013 to January 2018 were considered for study inclusion. Diagnosis of AHF was according to the European Society of Cardiology guidelines [19]. We included patients aged over 18 years who had stayed at the department more than 2 days. Exclusion criteria were as follows: (1) patients undergoing renal dialysis; (2) patients with eGFR less than 30 ml/(min·1.73m²) on admission; (3) patients with acute coronary syndrome, congenital heart disease, valvular heart disease or stroke; (4) patients with malignant tumor or severe infection; (5) patients with urinary tract infection or obstruction; (6) patient with incomplete medical records. 130 patients were excluded according to the inclusion and exclusion criteria. Thus, a total of 1235 AHF patients formed our study population. Two thirds of these patients were randomly assigned to the training set (n=823) to develop the predictive nomogram model, and the remaining 412 patients were assigned to the validation set to evaluate the performance of the model.

AKI during the first seven days of the hospitalization was the primary outcome of the study, which was defined based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [20].

The study protocol was approved by the Ethics Committee of Civil Aviation General Hospital.

Data Collection

Clinical and laboratory data of all the patients were obtained from the electronic medical records. Basic clinical data included age, gender, smoking status, personal history of coronary heart disease, hypertension, diabetes, hyperlipidemia, cerebrovascular disease, chronic kidney disease, and prior medications used. Laboratory variables included hemoglobin, white blood cells, platelet, albumin, fasting blood glucose, creatinine, brain natriuretic peptide (BNP), high-sensitivity C-reactive protein (Hs-CRP), uNGAL and uAGT. These variables were measured on admission in the core laboratory of Civil Aviation General Hospital. eGFR was calculated using the Cockcroft and Gault equation [21].

Statistical Analysis

Data were analyzed using SPSS 22.0 software (SPSS, Inc., Chicago, IL) and R software version 3.3.2 (<http://www.r-project.org>). Continuous variables were compared by Student's t test or Mann-Whitney U test depending on their distributions, while categorical variables were compared by Chi-square test. Distributions of continuous variables were tested by Kolmogorov-Smirnov. Multivariate logistic regression analysis was performed to screen the clinical significant predictors for CRS1 in the training set. Based on the clinical significant predictors, we developed a nomogram for predicting CRS1 in AHF patients using rms package in R software.

Nomogram validation comprised two activities: internal validation and external validation. Firstly, internal validation was performed via a bootstrap method with 1000 resamples. The discrimination ability of the nomogram was analyzed by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. And a calibration plot was derived to explore the agreement between predicted probabilities by the nomogram and the observed CRS1 rates. Secondly, external validation was performed in the validation set. The nomogram was used to assess each patient in the validation set. And then AUC and calibration plot were generated to assess the discriminative performance and predictive accuracy of the nomogram model. A two-sided $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics of the study cohort

Overall, 1235 eligible patients were included in the analysis, of which 391 (31.7%) patients developed AKI during the first seven days of the hospitalization. Fig. 1 showed the flow diagram of the study participants. There were no significant differences in basic clinical data and laboratory variables between the training set and validation set (Table 1). 256 (31.1%) out of 823 patients in the training set developed AKI, while 135 (32.8%) out of 412 patients in the validation set developed AKI. The AKI incidence between the two groups was similar.

Independent predictors of CRS1 in patients with AHF

In the training set, the univariate analysis revealed that age, gender, diabetes, chronic kidney diseases, albumin, fasting blood glucose, creatinine, eGFR, BNP, hs-CRP, uNGAL, uAGT and NYHA were associated with CRS1 occurrence (Table 2). These factors were included in the multivariate regression analysis to screen the significant predictors of CRS1. The multivariate logistic regression analysis results revealed that six variables, ie, age, diabetes, NYHA class, eGFR, hs-CRP and uAGT were independent predictors for CRS1 in patients with AHF (Table 3).

Construction of the predictive nomogram for CRS1 in patients with AHF

The predictive nomogram, shown in Fig. 2, was constructed based on the six independent predictors of CRS1.

Fig. 1. Flow diagram of enrollment of the study participants.

Each subtype within these variables was assigned a score on the point scale. After summing up the total score and locating it on the total point scale, we could draw a vertical line down to get the predicted probability of CRS1. The higher score of total points reflected a more probability of CRS1.

Internal validation of the predictive nomogram

When subjected to the internal validation, the predictive nomogram demonstrated a good discriminative ability with AUC 0.885 (95%CI: 0.862-0.908) (Fig. 3A). The calibration plot showed that the predicted probabilities of AKI by the nomogram reasonably approximated actual probabilities (Fig. 3B). The mean absolute error between the predicted and actual probabilities was 0.007 in the training set.

External validation of the predictive nomogram

External validation was accomplished by the comparisons between the nomogram predicted and actual probability for each patient in the validation set. In the validation set, the AUC of the predictive nomogram was 0.823 (95%CI: 0.777-0.870) (Fig. 4A). The calibration plot presented that there was a good agreement between predicted and actual probabilities, and the mean absolute error between the predicted and actual probabilities was 0.032 (Fig. 4B).

Clinical application of the nomogram

Hereby, we took two AHF patients as examples of the application of the nomogram. The first patient was aged 72 years (55 points) with diabetes (69 points). His NYHA class was IV (94 points). The levels of eGFR, hs-CRP and uNGAL were 60 ml/(min·1.73m²) (17 points), 19 mg/L (55 points), 152μg/g Cr (100 points), respectively. The nomogram score was calculated to be 390 points, and the probability of CRS1 was over 0.9. This patient was at very high risk of developing CRS1. And actually he developed CRS1 during the hospitalization. The second patient was aged 65 years (49 points) without diabetes (0 points). His NYHA class was III (73 points). The levels of eGFR, hs-CRP and uNGAL were 91 ml/(min·1.73m²) (8 points), 15 mg/L (44 points), 73μg/g Cr (32 points). The nomogram score was calculated to be 206

Table 1. Baseline Characteristics for patients in training set and validation set. Values are expressed as means ± SD, or median (25th-75th percentile), unless specified otherwise. NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs-CRP: high-sensitivity C-reactive protein; uNGAL: urinary neutrophil gelatinase-associated lipocalin; uAGT: urinary angiotensinogen; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CRS1: cardiorenal syndrome type 1

Characteristics	Training Set (n=823)	Validation Set (n=412)	P Value
Age	62.3±10.7	63.0±10.4	0.274
Gender, male, n(%)	496(60.3)	227(55.1)	0.082
Coronary Heart Diseases, n(%)	419(50.9)	198(48.1)	0.344
Hypertension, n(%)	401(48.7)	220(53.4)	0.121
Diabetes, n(%)	269(32.7)	151(36.7)	0.165
Hyperlipidemia, n(%)	185(22.5)	109(26.5)	0.122
Cerebrovascular disease, n(%)	118(14.3)	46(11.2)	0.121
Chronic Kidney Diseases, n(%)	156(19.0)	91(22.1)	0.194
NYHA class, n(%)			0.510
I	16(1.9)	9(2.2)	
II	38(4.6)	25(6.1)	
III	365(44.3)	173(42)	
IV	404(49.1)	205(49.8)	
LVEF(%)	41.6±11.3	42.7±12.5	0.120
Hemoglobin (g/L)	121.8±32.7	125.6±33.9	0.057
White Blood Cells (10 ⁹ /L)	9.6±2.5	9.4±2.1	0.163
Platelet (10 ⁹ /L)	216.8±55.4	219.4±59.8	0.449
Albumin (g/L)	30.6±10.2	31.2±11.6	0.352
Fasting blood glucose (mmol/L)	5.4±1.9	5.2±1.7	0.071
Creatinine (μmol/L)	107.2±33.7	103.8±30.9	0.086
eGFR ml/(min·1.73m ²)	67.9±23.2	66.1±23.3	0.199
BNP(ng/L)	1150.7±440.9	1193.9±435.7	0.103
hs-CRP(mg/L)	12.6±7.2	13.3±6.8	0.101
uNGAL (μg/g Cr)	57.9(21.6-224.9)	45.9(20.7-215.6)	0.123
uAGT (μg/g Cr)	40.8(11.3-162.5)	43.8(12.3-175.6)	0.157
Medications			
ACEI/ARB, n(%)	312(37.9)	173(42)	0.166
Aldosterone antagonists, n(%)	193(23.5)	85(20.6)	0.263
β-blockers, n(%)	205(24.9)	120(29.1)	0.113
Diuretics, n(%)	436(53.0)	235(57.0)	0.177
Statins, n(%)	105(12.8)	46(11.2)	0.420
Nitrates, n(%)	176(21.4)	105(25.5)	0.105
Digoxin, n(%)	171(20.8)	73(17.7)	0.203
CRS1, n(%)	256(31.1)	135(32.8)	0.554

Table 2. Univariate analyses of factors associated with CRS1 in the training set. Values are expressed as means $\pm$ SD, or median (25th-75th percentile), unless specified otherwise. CRS1: cardiorenal syndrome type 1; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs-CRP: high-sensitivity C-reactive protein; uNGAL: urinary neutrophil gelatinase-associated lipocalin; uAGT: urinary angiotensinogen; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker

Characteristics	CRS1 (n=256)	non- CRS1 (n=567)	P Value
Age	64.81 $\pm$ 10.45	61.09 $\pm$ 10.62	< 0.001
Gender, male, n(%)	168(65.6)	328(57.8)	0.035
Coronary Heart Diseases, n(%)	125(48.8)	294(51.9)	0.422
Hypertension, n(%)	120(46.9)	281(49.6)	0.476
Diabetes, n(%)	155(60.5)	114(20.1)	< 0.001
Hyperlipidemia, n(%)	68(26.6)	117(20.6)	0.059
Cerebrovascular disease, n(%)	36(14.1)	82(14.5)	0.880
Chronic Kidney Diseases, n(%)	80(31.3)	76(13.4)	< 0.001
Hemoglobin (g/L)	119.8 $\pm$ 31.1	122.7 $\pm$ 33.8	0.243
NYHA class, n(%)			< 0.001
I	0(0)	16(2.8)	
II	10(3.9)	28(4.9)	
III	82(32)	283(49.9)	
IV	164(64.1)	240(42.3)	
LVEF(%)	40.8 $\pm$ 11.3	42.0 $\pm$ 12.5	0.204
White Blood Cells (10 ⁹ /L)	9.4 $\pm$ 2.6	9.7 $\pm$ 2.3	0.108
Platelet (10 ⁹ /L)	214.7 $\pm$ 56.3	217.7 $\pm$ 58.7	0.485
Albumin (g/L)	28.9 $\pm$ 10.5	31.4 $\pm$ 11.7	0.004
Fasting blood glucose (mmol/L)	5.6 $\pm$ 1.7	5.3 $\pm$ 1.6	0.018
Creatinine (μ mol/L)	110.8 $\pm$ 35.7	105.6 $\pm$ 30.6	0.032
eGFR ml/(min $\cdot$ 1.73m ²)	64.2 $\pm$ 22.5	69.6 $\pm$ 23.4	0.002
BNP (ng/L)	1201.4 $\pm$ 440.9	1127.8 $\pm$ 435.7	0.026
hs-CRP (mg/L)	15.0 $\pm$ 7.54	11.5 $\pm$ 6.82	< 0.001
uNGAL (μ g/g Cr)	57.6(21.5-219.1)	27.9(11.3-104.8)	< 0.001
uAGT (μ g/g Cr)	75.9(31.6-198.5)	19.3(10.2-93.8)	< 0.001
Medications			
ACEI/ARB, n(%)	106(41.4)	206(36.3)	0.165
Aldosterone antagonists, n(%)	65(25.4)	128(22.6)	0.377
β -blockers, n(%)	61(23.8)	144(25.4)	0.630
Diuretics, n(%)	132(51.6)	304(53.6)	0.585
Statins, n(%)	25(9.8)	80(14.1)	0.084
Nitrates, n(%)	50(19.5)	126(22.2)	0.383
Digoxin, n(%)	58(22.7)	113(19.9)	0.372

Table 3. Multivariate logistic regression analysis of variables predicting CRS1. CRS1: cardiorenal syndrome type 1; NYHA: New York Heart Association; eGFR: estimated glomerular filtration rate; hs-CRP: high-sensitivity C-reactive protein; uAGT: urinary angiotensinogen

Variables	β coefficient	SE	Wald	P Value	OR	95%CI
Age	0.032	0.009	11.315	0.001	1.032	1.013-1.052
Diabetes	2.260	0.222	103.748	< 0.001	9.579	6.202-14.797
NYHA class						
I	Reference					
II	1.200	1.283	0.875	0.349	3.320	0.269-41.002
III	2.390	1.168	4.185	0.041	10.912	1.106-107.706
IV	3.084	1.166	6.992	0.008	21.844	2.221-214.833
eGFR	-0.010	0.004	4.836	0.028	0.990	0.982-0.999
hs-CRP	0.095	0.014	42.689	< 0.001	1.099	1.069-1.131
uAGT						
<25	Reference					
25~50	-0.308	0.611	0.254	0.614	0.735	0.222-2.433
50~100	-1.057	0.586	3.251	0.071	0.348	0.11-1.096
>100	2.211	0.445	24.676	< 0.001	9.122	3.813-21.821

points, and the probability of CRS1 was less than 0.1. The second patient was at very low risk of developing CRS1. And actually he didn't develop CRS1 during the hospitalization.

Fig. 2. Nomogram model for predicting the risk of CRS1 in patients with AHF.

Fig. 3. Internal validation of nomogram in training set. (A) Discrimination: AUC of the ROC curve was 0.885 (95%CI: 0.862-0.908). (B) Nomogram calibration plot. Mean absolute error = 0.007; mean squared error = 0.00011; 0.9 quantile of absolute error = 0.017.

Fig. 4. External validation of nomogram in validation set. (A) Discrimination: AUC of the ROC curve was 0.823 (95%CI: 0.777-0.870). (B) Nomogram calibration plot. Mean absolute error = 0.032; mean squared error = 0.00153; 0.9 quantile of absolute error = 0.067.

Discussion

CRS1, characterized by acute worsen cardiac function leading to AKI, is closely associated with a high morbidity and mortality in patients with AHF [22]. Early recognition of patients at high risk of CRS1 may assist disease management, enhance patient-clinician communications, and contribute to the prognosis of the patients. However, currently there is still no early or accurate diagnostic model of CRS1 in AHF patients. The utility of routinely accessible clinical variables to detect CRS1 early enough has attracted scientific interest. In this study, we aimed to develop and validate a predictive nomogram for the risk of CRS1 in patients with AHF.

The nomogram construction began with the identification of independent predictive factors for CRS1 in AHF patients. In our study, multivariate logistic regression analysis results revealed that age, diabetes, eGFR, NYHA class, hs-CRP and uAGT were independent predictors of CRS1. Consistent with previous studies, our study revealed that advanced age, diabetic state, and lower levels of basal eGFR could contribute to the development of CRS1 [23, 24]. Additionally, NYHA classification, the most widely used system to assess the functional capacity and predict prognosis in patients with heart failure, was found to be a significant predictor of CRS1 in our study. Zhang W et al. [25] found that 90% of chronic heart failure patients who experienced AKI were with NYHA class III/IV. Zhou LZ et al. [26] found that 58.9% of AHF patients developing CRS1 were NYHA class IV. In our study, NYHA class III/IV accounted for 96.1% of the CRS1 patients. And patients with NYHA class III/IV were more likely to suffer from AKI compared those with NYHA class I.

Hs-CRP, a well-recognized sensitive marker of systemic inflammation, can activate the clotting system and cause the impairment of oxidant defenses leading to the endothelial dysfunction [27]. Endothelial dysfunction was proposed as one of the contributing mechanisms to AKI development [28, 29]. Thus, elevated hs-CRP might be a potential marker of AKI. Shacham Y et al. [30] identified that hs-CRP was an independent predictor of AKI in ST elevation myocardial infarction patients undergoing primary percutaneous intervention. However, Chen TH et al. [31] found that hs-CRP was not an independent predictor of AKI in patients admitted to the coronary care unit, though patients who developed AKI were with higher hs-CRP levels. In the present study, hs-CRP was of predictive significance for CRS1 in AHF patients. The inconsistent findings probably resulted from the different included participants.

AGT, a principal substrate of the local intrarenal renin-angiotensin system (RAS), is mainly formed in the proximal tubule cells and secreted into the tubule lumen [32, 33]. Increasing evidence has suggested the strong predictive role of uAGT in the initiation and progression of AKI, particularly in the setting of heart failure. Yang et al. [13] found that uAGT was closely associated with the increased risk of AKI, and confirmed that uAGT had superior performance in predicting AKI, compared with uNGAL and NT-pro-BNP in patients with AHF. Chen et al.'s study [10] revealed that uAGT outperformed other kidney biomarkers such as uNGAL, uIL-18 and uKIM-1 for the prediction of AKI progression in the setting of AHF. Similar to previous studies, our study supported the strong predictive value of uAGT for the risk of CRS1. uNGAL, a 25-kDa transport protein expressed by neutrophils and epithelial cells, was another biomarker of kidney injury [34]. Several studies aimed to explore the utility of uNGAL in predicting CRS1 in patients with AHF, but gained inconsistent conclusions [35-38]. In the present cohort, uNGAL was closely associated with the risk of CRS1, but not an independent predictor of CRS1 by multivariate analysis.

To our best knowledge, this is the first nomogram for predicting the risk of CRS1 in patients with AHF. The nomogram based on six feasible and cost-effectiveness variables, enables easy calculation of individualized CRS1 risk estimates for patients with AHF. The AUC for the predictive nomogram was 0.885 in the training set and 0.823 in the validation set. The calibration plots showed that the nomogram prediction was well fitted to the actual probability of CRS1 on both internal and external validation. These results suggested that

the predictive nomogram had sufficient discriminative power and good accuracy to estimate CRS1 in AHF patients. Besides, compared with Zhou et al.'s risk score [26] (c-index = 0.859) predicting AKI in patients with AHF, our nomogram model exerted better discrimination ability (c-index = 0.885) and was validated in a larger cohort for the CRS1 prediction in AHF patients.

Our study had several limitations as well. First, not all the potential predictors, such as IL-18, and KIM-1, for CRS1 are studied, as these markers are not routinely tested for AHF patients in clinical practice. Second, the study was a single-center study. Although both training set and validation set were from the same institution, this is an acceptable method of nomogram development and validation when external cohort is not available. However, the nomogram needs to be validated in the other centers to test its generalizability. Third, there were no follow-up measurements of the variables incorporated into the nomogram. Yet the aim of the study was to estimate the risk of CRS1 based on the clinical characteristics on admission in order to initiate timely intervention.

Conclusion

In conclusion, age, diabetes, NYHA class, eGFR, hs-CRP and uAGT were strongly associated with the risk of CRS1 in AHF patients. The present nomogram constructed based on these six feasible clinical variables, could predict the individualized risk of CRS1 with good accuracy and discrimination. The proposed nomogram would be helpful for clinicians in making decisions and implementing interventions with clinical practical utility.

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Disclosure Statement

The authors declare that they have no competing interests.

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