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ORIGINAL RESEARCH

Development and Validation of a Risk Score for Prediction of Acute Kidney Injury in Patients With Acute Decompensated Heart Failure: A Prospective Cohort Study in China

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***Background*—**Although several risk factors for acute kidney injury (AKI) have been identified, early detection of AKI in acute decompensated heart failure patients remains a challenge. The aim of this study was to develop and validate a risk score for early prediction of AKI in acute decompensated heart failure patients.

***Methods and Results*—**A total of 676 consecutive acute decompensated heart failure participants were prospectively enrolled from 6 regional central hospitals. Data from 507 participants were analyzed. Participants from 4 of the 6 hospitals (n=321) were used to develop a risk score and conduct internal validation. External validation of the developed risk score was conducted in participants from the other 2 hospitals (n=186). Sequential logistic regression was used to develop and validate the risk score. The c statistic and calibration plot were used to assess the discrimination and calibration of the proposed risk score. The overall occurrence of AKI was 33.1% (168/507). The risk score, ranging from 0 to 55, demonstrated good discriminative power with an optimism-corrected c statistic of 0.859. Similar results were obtained from external validation with c statistic of 0.847 (95% CI 0.819-0.927). The risk score had good calibration with no apparent over- or under-prediction observed from calibration plots.

***Conclusions*—**The novel risk score is a simple and accurate tool that can help clinicians assess the risk of AKI in acute decompensated heart failure patients, which in turn helps them plan and initiate the most appropriate disease management for patients in time. **(*J Am Heart Assoc*. 2016;5:e004035 doi: 10.1161/JAHA.116.004035)**

Key Words: acute decompensated heart failure • acute kidney injury • risk prediction • risk stratification

Acute decompensated heart failure (ADHF) is one of the leading causes of hospitalization. More than 30% of patients hospitalized for ADHF experience acute kidney injury (AKI),[1-8] which is independently associated with increased risk of morbidity and mortality.[9,10] The clinical importance of the coexistence of acute cardiac and renal dysfunction, known as acute cardiorenal syndrome (CRS), and its management have received great attention recently.[11-13]

The poor prognosis of acute CRS makes the identification of patients at high risk especially important. However, early diagnosis of acute CRS has remained elusive due to restrictions on using serum creatinine or urine output for diagnosis of AKI.[14] The current diagnostic paradigm for AKI relies largely on biomarkers of renal function (serum creatinine and urine output) that have been in clinical use for over 50 years but are known to be insensitive and slow to change after kidney injury, often leading to a late and inaccurate diagnosis of AKI with resultant adverse outcomes.[9,10,14] Therefore, the current paradigm of AKI diagnosis needs to be reassessed in light of scientific advances in the understanding of the pathobiology of AKI facilitated in part by recent biomarker discovery programs.[15]

Although it has been the goal of several studies to develop kidney injury biomarkers (such as neutrophil gelatinase-associated lipocalin [NGAL] and urinary angiotensionogen [uAGT])[13,16-22] for early detection of AKI before occurrence of

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Accompanying Data S1, Tables S1 through S5 and Figures S1 through S6 are available at http://jaha.ahajournals.org/content/5/11/e004035/DC1/embed/inline-supplementary-material-1.pdf

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renal dysfunction, these studies have yielded varied performance. This suggests that a single biomarker (or single type of biomarkers) is not sufficient for the evaluation of clinical settings such as CRS.[15,17] Therefore, reformulating the predictive approach of AKI, ie, a multimarker approach, is more likely to be of greater use.[23] The major purpose of our study is to incorporate both clinical risk factors and the novel kidney injury biomarkers for such prediction that we can predict CRS early and improve the risk reclassification in this disorder. Precisely, we will develop and validate a risk score that can identify patients with either a very high or a very low probability of developing AKI using only baseline characteristics and effective urine biomarkers before a detectable change in serum creatinine in ADHF patients.

Methods

Study Population and Database

A total of 676 consecutive ADHF participants, aged 18 to 80 years, were prospectively enrolled between September 2011 and August 2014 from 6 regional central hospitals located in 5 cities in China. All participants had given informed consent for this specific study. Among these participants, 169 were excluded according to exclusion criteria (Figure S1). The remaining 507 participants formed our study population, of which 321 participants from 4 of the 6 hospitals served as the development cohort to develop the risk score. The remaining 186 participants from the other 2 hospitals served as independent validation cohort. ADHF was diagnosed based on the European Society of Cardiology criteria.[24] Estimated glomerular filtration rate (eGRF) was determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[25] All participants had consecutive measurements of serum creatinine and urine biomarkers every day during the first 7 days of hospitalization. The values on the first day were used to develop the risk score for early prediction of AKI, and serum creatinine values on other days were used to assess the development of AKI.

This research was approved by the Institutional Review Board of the Guangdong Provincial Institute of Nephrology and the ethics committees of the participating hospitals before recruiting patients.

Outcome Definition

The primary outcome was the development of AKI. It was defined as an increase in serum creatinine by 26.5 μmol/L (0.3 mg/dL) within 48 hours of admission, or a 50% increase in serum creatinine from preadmission level (mean of at least 3 measurements over a 6-month period before admission) within 7 days of admission according to the KDIGO Clinical Practice Guidelines for Acute Kidney Injury.[26] We did not use urine output criteria (ie, <0.5 mL/kg per hour for >6 hours) for AKI diagnosis because of lack of practicality in measurement when an indwelling urinary catheter was not present.

Sample Size and Missing Data

Sample size determination for observational study is difficult, especially in multiple regression model settings. We had used the rule of thumb recommended by Peduzzi et al[27] and Harrell et al,[28] namely, events per variable (EPV) being 10 or greater under this circumstance. We considered about 5 to 8 significant clinical factors and 2 to 3 biomarkers in developing a model. This would have required us to recruit a minimum of 110 (11×10) participants who had events to predict the development of AKI.

There were 2 cases with incomplete measurements. We performed simple imputation for these 2 cases. One case with missing serum albumin was imputed by mean, and the other with missing N-terminal pro-B-type natriuretic peptide (NT-proBNP) by median because of skewness. All analyses were performed based on imputed complete cases.

Statistical Analysis

We took 2 steps to develop the risk model based on the development cohort. The first step was to select meaningful clinical risk factors (nonurine markers) by logistic regression with backward elimination. Clinical candidate predictors significant at $P<0.1$ in univariate logistic regression models were considered for backward elimination. In this step, a clinical model with clinical factors was developed. Then, urine biomarkers (urine albumin-to-creatinine ratio [UACR], urinary NGAL [uNGAL], and uAGT) were evaluated sequentially based on this clinical model. Category-free (continuous) net reclassification index (NRI), integrated discrimination improvement (IDI),[29] and added value of c statistics were used to quantify the additional contribution of these urine biomarkers to risk reclassification.

To develop the risk score, the scoring method similar to that of Sullivan et al,[30] was employed based on the developed risk model. The predictive accuracy of the risk score was assessed by both discrimination measured by c statistic[31] and calibration evaluated by Hosmer-Lemeshow chi-squared statistic[32] and calibration plot, a plot of observed proportions versus predicted probabilities. Bootstrapping technique was used to adjust for overfitting and overoptimistic model performance. An optimism-corrected c statistic using 1000 bootstrap samples created with replacement was reported. Furthermore, external validation of the risk score was conducted to assess the stability of the model.

Predefined interactions (sex×preexisting chronic kidney disease [pre-CKD], pre-CKD×uNGAL, and pre-CKD×uAGT) between predictors and potential nonlinear association of included biomarkers were also examined at the 5% significance level. Sensitivity analysis was conducted to assess the influence of the 2 incomplete measures by leaving the corresponding 2 cases out. All analyses were done with SAS (SAS Institute Inc, Cary, NC, version 9.4). A 2-sided $P<0.05$ was considered statistically significant.

The reporting of the present study closely follows the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[33] Additional study methods are described in Data S1.

Results

The flow of participants is presented as Figure S1. Among the 507 participants, 168 (33.1%) developed AKI during the first 7 days of hospitalization, of whom 108 (64.3%) developed AKI during the first 48 hours of hospitalization. A total of 113 (35.2%) participants developed AKI during hospitalization in the development cohort, and 55 (29.6%) in the validation cohort. Sixty-one (12.0%) patients died during hospitalization. Overall, the mean age of the participants was 65.2 years, and 63.1% were male. For the clinical conditions, participants with hypertension, diabetes mellitus and pre-CKD accounted for 49.9%, 25.4%, and 26.2%, respectively. Table 1 shows the characteristics of eligible participants for both the development and validation cohort recorded on admission. The baseline characteristics of the validation cohort were generally similar to those of the development cohort, although the validation cohort was drawn from an independent group of participants. Two cases with incomplete measurements were imputed as described in the Sample Size and Missing Data section. Baseline characteristics outlining those who developed versus those who did not develop AKI were presented in Table S1.

Risk Score Development

The clinical model, including age, sex, pre-CKD, serum albumin (ALB), and NT-proBNP (Table 2), had a c statistic of 0.767 (95% CI 0.714-0.820). The first urine biomarker added to the clinical model was uAGT, with a category-free NRI of 0.809 ($P<0.001$) and an IDI of 0.169 ($P<0.001$). The second urine biomarker added to the clinical model with uAGT was uNGAL, with a category-free NRI of 0.293 ($P=0.012$) and an IDI of 0.023 ($P=0.011$). However, UACR did not improve model prediction significantly, nor did it make an additional contribution to risk reclassification (Table S2). Thus, the risk model was obtained by adding uAGT and uNGAL rather than UACR to the clinical model. Neither nonlinearity nor interactions were found significant. The risk model has excellent discriminative power with a c statistic of 0.874 (95% CI 0.835-0.913), significantly larger than that of the clinical model (DeLong test, $P<0.001$).

Scores based on the risk model for all predictors are presented in Table 3. The estimated predicted probability of developing AKI during the first 7 days after admission for an individual ADHF patient according to the proposed risk score is expressed as

$$\mathrm{p(AKI)} = \frac{1}{1 + \mathrm{e}^{-(-4.027+0.115*\mathrm{totalriskscore})}}$$

where −4.027 and 0.115 are the intercept and slope coefficients of the regression, respectively. The total risk score ranges from a minimum value of 0 (lowest risk) to a maximum value of 55 (highest risk), with corresponding estimated predicted probabilities of developing AKI ranging from 1.8% to 90.9% (Table S3). The optimism-corrected c statistic of the risk score in the development cohort, by the bootstrapping technique, was 0.859.

To illustrate the application of the risk score, consider a 60-year-old woman with ADHF, preexisting CKD, ALB of 40 g/L, NT-proBNP of 3200 pg/mL, uNGAL of 65 μg/g Cr, and uAGT of 35 μg/g Cr. The total risk score she gets is 0+2+9+0+0+6+13=30 from Table 3, and the estimated predicted probability that she will develop AKI is 36.0% according to Table S3. An easy-to-use online tool (http://www.echobelt.org/risk/) as well as an Excel tool was developed whereby an individual's underlying risk of AKI can be estimated by entering the individual's own characteristics.

Validation of Risk Score

In an independent validation cohort, the c statistics of the developed risk score was 0.847 (95% CI 0.795-0.910). The receiver operating characteristics curves (ROCs) of the clinical model, the risk model, the risk score, and models with only uNGAL or uAGT are shown in Figure 1. The calibration plots for both cohorts show the close agreement between predicted and observed risk of AKI, with no apparent over- or under-prediction (Figure 2). AKI rates from both development and validation cohorts are also concordant with each other.

Clinical Implications of the Risk Score

We divided the risk scores into 4 groups, that is, low risk (0-24 points), moderate risk (25-34 points), high risk (35-44 points), and very high risk (45-55 points) (Figure 3), according to the quartiles of estimated risk, to enhance the clinical utility of the risk score. In the development and validation cohorts AKI was

Table 1. Characteristics for Included Patients in Development and Validation Cohorts

	Development Cohort (n=321)	Validation Cohort (n=186)	All (n=507)
Demographics			
Mean (SD) age, y	64.9 (15.5)	65.7 (14.0)	65.2 (15.0)
Male	216 (67.3)	104 (55.9)	320 (63.1)
Preexisting clinical conditions			
Hypertension	169 (52.6)	84 (45.2)	253 (49.9)
Diabetes mellitus	86 (26.8)	43 (23.1)	129 (25.4)
Pre-CKD*	90 (28.0)	43 (23.1)	133 (26.2)
Prior hospitalization for HF	165 (51.4)	96 (51.6)	261 (51.5)
Primary causes of heart failure			
Ischemic heart disease	165 (51.4)	106 (57.0)	271 (53.5)
Hypertension	44 (13.7)	21 (11.3)	65 (12.8)
Rheumatic heart disease	46 (14.3)	24 (12.9)	70 (13.8)
Cardiomyopathy	42 (13.1)	20 (10.8)	62 (12.2)
Other	24 (7.5)	15 (8.1)	39 (7.7)
Characteristics on admission			
LVEF <45%	155 (48.3)	79 (42.5)	234 (46.2)
NYHA, class IV	151 (47.0)	92 (49.5)	243 (47.9)
Median (IQR) NT-proBNP, pg/mL	5500 (2292-9000)	4235 (2271-8540)	5099 (2284-9000)
Mean (SD) SBP, mm Hg	125.2 (24.1)	130.6 (24.4)	127.2 (24.3)
Mean (SD) DBP, mm Hg	73.7 (14.7)	78.1 (16.7)	75.3 (15.6)
Mean (SD) serum creatinine, μmol/L	110.4 (52.9)	105.2 (42.1)	108.5 (49.3)
Mean (SD) serum albumin, g/L	32.2 (5.9)	35.8 (5.9)	33.5 (6.1)
Mean (SD) hemoglobin, g/L	123.4 (26.0)	125.1 (22.9)	124.0 (24.9)
Treatment before admission			
Use ACEI/ARB preadmission	107 (33.3)	37 (19.9)	144 (28.4)
Mean (SD) drug index of ACEI/ARBc	4.2 (1.2)	4.5 (1.0)	4.3 (1.2)
Use spironolactone	109 (34.0)	54 (29.0)	163 (32.1)
Mean (SD) drug index of spironolactone	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)
Mean (SD) drug score of RAAS blocker	5.1 (1.3)	5.8 (1.1)	5.3 (1.2)
Use diuretic preadmission	124 (38.6)	59 (31.7)	183 (36.1)
Use of high-dose diuretic	8 (2.5)	2 (1.1)	10 (2.0)
Biomarker measurement			
Median (IQR) UACR, mg/g Cr	100.6 (27.9-314.8)	65.66 (16.98-191.65)	84.2 (23.2-245.2)
Median (IQR) uNGAL, μg/g Cr	53.4 (22.2-174.9)	32.55 (15.17-89.31)	42.5 (20.1-141.2)
Median (IQR) uAGT, μg/g Cr	39.31 (10.7-147.1)	34.85 (14.09-104.07)	37.4 (10.7-147.1)
Prognosis			
AKI, n (%)	113 (35.2)	55 (29.6)	168 (33.1)

Values are numbers (percentages) unless stated otherwise. AKI indicates acute kidney injury; pre-CKD, preexisting chronic kidney disease; DBP, diastolic blood pressure; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio; uAGT, urinary angiotensionogen; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

*Defined as preadmission eGFR <60 mL/min per 1.73 m^2. Preadmission eGFR is the mean of at least 3 measurements over a 6-month period before admission.

Table 2. Univariate and Multivariate Logistic Regression Analysis of Candidate Risk Factors for AKI (Development Cohort, n=321)

	Univariate Analysis		Clinical Model		Risk Model*		
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	Coefficient	OR (95% CI)	*P* Value
Age	1.03 (1.02-1.05)	<0.001	1.03 (1.01-1.05)	0.002	0.0141	1.01 (0.99-1.04)	0.22
Sex, male	0.91 (0.55-1.51)	0.72	0.83 (0.48-1.45)	0.516	0.1679	1.18 (0.62-2.26)	0.61
Hypertension	1.82 (1.09-3.04)	0.02					
Diabetes mellitus	2.43 (1.45-4.09)	0.001					
pre-CKD	5.47 (3.18-9.39)	<0.001	4.15 (2.36-7.28)	<0.001	1.2200	3.39 (1.73-6.65)	<0.001
Prior hospitalization for HF	1.28 (0.79-2.06)	0.31					
LVEF <45%	1.16 (0.72-1.87)	0.53					
NYHA, class IV	2.24 (1.39-3.63)	0.001					
ln-NT-proBNP†	1.58 (1.23-2.04)	<0.001	1.36 (1.04-1.77)	0.023	0.2320	1.26 (0.93-1.72)	0.14
SBP	1.01 (1.00-1.02)	0.06					
DBP	1.01 (1.00-1.03)	0.12					
Serum creatinine†	1.01 (1.01-1.02)	<0.001					
Serum albumin	0.92 (0.88-0.96)	0.001	0.94 (0.90-0.98)	0.007	−0.0117	0.99 (0.93-1.05)	0.69
Hemoglobin	0.99 (0.98-0.99)	0.003					
Use ACEI/ARB preadmission	1.16 (0.71-1.91)	0.55					
Use diuretic preadmission	1.22 (0.75-1.99)	0.42					
ln-UACR†	1.63 (1.38-1.93)	<0.001					
ln-uNGAL†	2.01 (1.65-2.44)	<0.001			0.3439	1.41 (1.12-1.78)	<0.001
ln-uAGT†	1.99 (1.66-2.37)	<0.001			0.5532	1.74 (1.43-2.11)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CI, confidence interval; DBP, diastolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; pre-CKD, preexisting chronic kidney disease; SBP, systolic blood pressure; UACR, urine albumin to creatinine ratio; uAGT, urinary angiotensionogen; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

*Intercept=−7.325.

†Natural logarithm transformed values of those variables were used in developing risk model.

present in, respectively, 9.3% and 9.5% participants of the low-risk group, 31.1% and 40.0% of the moderate-risk group, 63.9% and 66.7% of the high-risk group, and 83.7% and 78.6% of the very high-risk group. As Figure 3 shows, the risk of developing AKI is highly and positively associated with the risk scores (Pearson contingency coefficient=0.517, *P* for trend <0.001). We also performed subgroup analysis according to LVEF. The c statistics of the risk score for participants with LVEF <45% and ≥45% are 0.849 (95% CI 0.786-0.912) and 0.870 (95% CI 0.811-0.928), respectively. The discrimination power of 2 subgroups was similar, suggesting that the risk score was applicable for both subgroups of participants.

The generated risk score was also correlated with the presence and stage of AKI. The score was significantly higher in those patients who developed AKI than those who did not. Higher risk score was observed in patients with higher stage of AKI (Spearman rank correlation coefficient, r=0.59, P<0.001, Figure S2). In addition, the discriminatory ability of the score for predicting death was also good, with a c statistic of 0.815 (95% CI 0.762-0.867) (Figure S3).

Furthermore, we also developed a clinical score based on the clinical model with prognostic factors presented in Table 2. The clinical score had an acceptable c statistic of 0.729 (95% CI 0.672-0.786). Validation of the clinical score was performed on the development data set with bootstrap internal validation and the validation data set as external validation, with c statistic of 0.730 (95% CI 0.673-0.786) and 0.742 (95% CI 0.666-0.818), respectively. Risk score for each variable is given in Table S4. The ROCs and calibration plots, as well as risk categories, are presented in Figures S4 through S6.

Sensitivity Analysis

First, to assess the influence of the 2 incomplete measures, we derived a risk model on a complete data set by leaving the corresponding 2 cases out. The discrimination power (c statistic 0.873, 95% CI 0.834-0.912) was almost the same as that from imputed complete cases. Further, applying the risk score to all participants yielded a c statistic of 0.855 (95% CI

Table 3. Risk Score for Single Risk Factors Associated With Developing AKI in ADHF Patients (Development Cohort)*

Risk Factor	Score	c-Statistic for Single Variable
Age, y		0.638 (0.574-0.701)
≤55	0	
56 to 65	2	
66 to 75	3	
76 and older	5	
Sex		0.514 (0.460-0.568)
Male	1	
Female	0	
Pre-CKD		0.680 (0.627-0.732)
Yes	9	
No	0	
Serum albumin, mmol/L		0.640 (0.576-0.704)
≤35	1	
>35	0	
NT-proBNP, pg/mL†		0.635 (0.572-0.698)
<5578	0	
≥5578	5	
uNGAL, μg/g Cr†		0.762 (0.707-0.816)
<25	0	
25 to 49.99	5	
50 to 99.99	6	
≥100	11	
uAGT, μg/g Cr†		0.814 (0.767-0.861)
<25	0	
25 to 49.99	13	
50 to 99.99	16	
≥100	23	

ADHF indicates acute decompensated heart failure; AKI, acute kidney injury; Pre-CKD, preexisting chronic kidney disease; UACR, urine albumin-to-creatinine ratio; uAGT, urinary angiotensionogen; uNGAL, urinary neutrophil gelatinase-associated lipocalin.
*The highest observed total risk score of 55 coincides with the highest theoretical risk score.
†Categories and scores of those variables are present according to their untransformed value for clinical use.

0.820-0.890), which was similar to that from the development cohort, suggesting high stability of the risk score. We also conducted sensitivity analysis to assess the single biomarker discriminative power by adding a single biomarker to the clinical model. The results are presented in Table S5. Briefly, the final risk model had the lowest AIC and highest c statistic in the development data set. Furthermore, because of the correlation between pre-CKD and eGFR, eGFR was not selected during the backward selection. Thus, we kept the final risk model with pre-CKD.

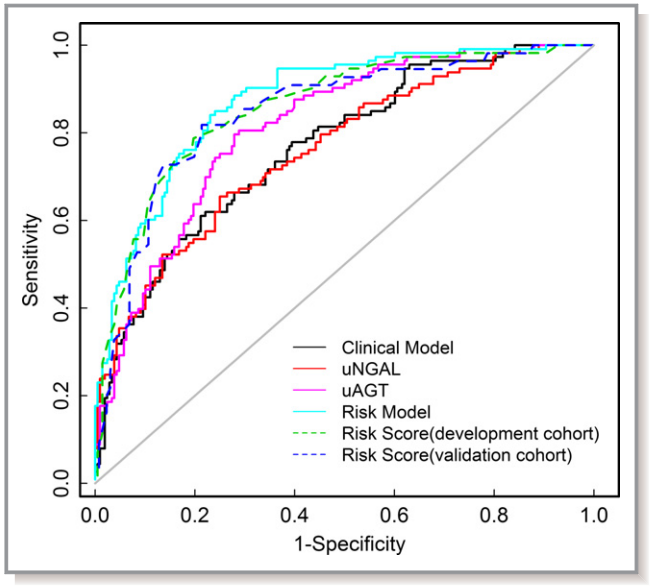

Figure 1. Receiver operator characteristic curves showing area under the curve for AKI in ADHF patients. Receiver operator characteristic curves showing area under the curve for clinical model alone, 0.765; uNGAL, 0.762; uAGT, 0.814; risk model, 0.874; risk score in development cohort, 0.859; risk score in validation cohort, 0.847.

Discussion

Main Finding

We have developed and validated a clinical scoring system to identify patients at a very high as well as a very low risk of

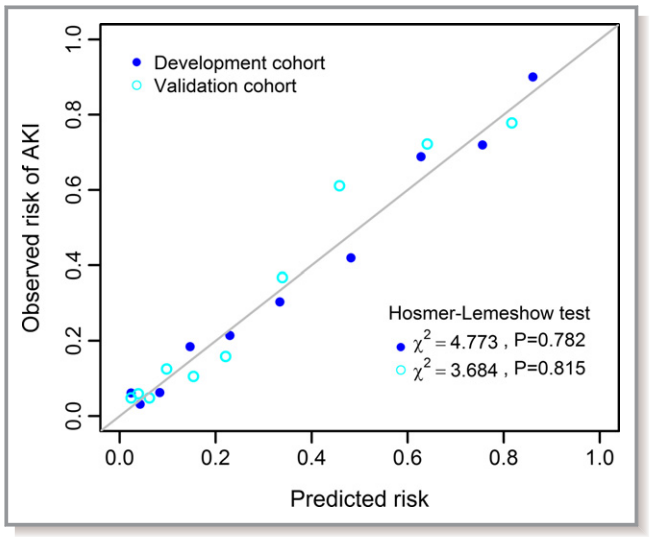

Figure 2. Calibration plot of observed vs predicted fracture risk for developing AKI during the first 7 days of hospitalization. Hosmer-Lemeshow chi-squared statistic is shown for the risk score in both development and validation cohorts. The points and circles indicate the observed frequencies by decile of predicted probability.

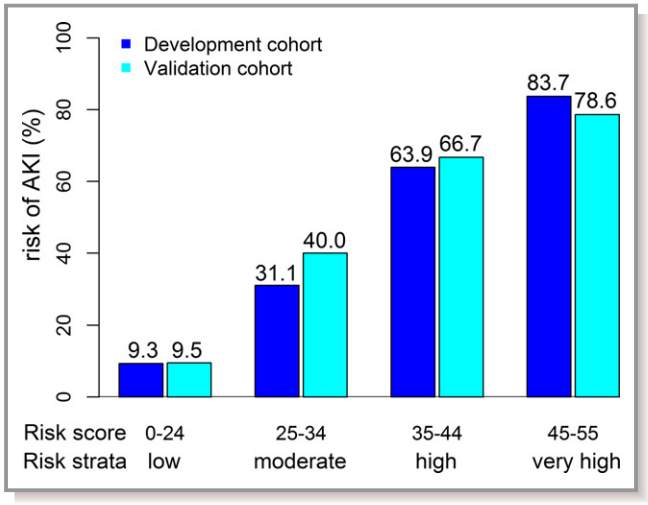

Figure 3. Risk levels according to the risk score in development and validation cohorts. Risks were categorized into low risk (0-24 points), moderate risk (25-34 points), high risk (35-44 points), and very high risk (45-55 points). Higher points means higher risk of developing AKI in patients with ADHF; *P* for trend <0.001.

developing AKI before a detectable change in serum creatinine in ADHF patients. The risk score was derived from a risk model including 5 clinical factors and 2 urine biomarkers. The clinical risk factors in the model were similar to those in previous reports.[34,35] Two selected biomarkers, uAGT and uNGAL, were highly predictive. The proposed risk score shows high discriminant power (optimism-corrected c statistic of 0.859) and is strongly supported by external validation (c statistics of 0.847). To our knowledge, this is the first clinical scoring system derived and validated for early prediction of AKI in ADHF patients incorporating clinical risk factors and novel kidney injury biomarkers.

Need for Early Predicting AKI in ADHF

Coexistence of ADHF and AKI, namely acute CRS, is a serious clinical condition associated with significantly increased morbidity and mortality in patients with heart failure.[10,36] A major barrier to improving clinical outcomes in ADHF patients is the lack of ability to identify patients at high-risk of CRS early enough to initiate interventions.[37] The clinical benefits of an early diagnosis of AKI have not been fully realized due to the restriction of using serum creatinine for diagnosis. This restriction often leads to diagnostic delays and potential misclassification of actual injury status and provides little information regarding underlying cause. Actually, all successful therapeutic approaches in animal models used in patients have yielded disappointing results.[38] Major reasons are the scarcity of early biomarkers for AKI and consequent unacceptable delay in initiating treatment regimens.[15]

AKI is a major contributor to poor patient outcomes. The International Society of Nephrology (ISN)'s 0by25 (zero preventable deaths by 2025) initiative aims to eliminate preventable deaths from AKI by 2025 by calling for global strategies that permit timely diagnosis and treatment of potentially reversible AKI.[39] As Mehta et al addressed in the Future Perspective Section, "the effect of AKI on morbidity and mortality will be shaped by advances in methods to detect AKI earlier in the disease course."[39] Because early detection of AKI is helpful in identifying early kidney injury and preventing the progression of the kidney damage, our work may provide the first step forward to avoid harm to the kidney and devise early preventive strategies in CRS.

Clinical and Policy Implications

The present study derived and validated a potential clinical prediction tool rather than a decision rule. It is to aid the attending physician who will make the clinical decision. The factors incorporated in the proposed risk score are readily available data recorded on admission or from routine medical examination. Both uAGT and uNGAL are accepted and utilized biomarkers of kidney injury. To date, clinical studies that use the biomarkers to predict acute CRS yield only modest performance in general.[40,41] Individual prediction of AKI remains a challenge in the setting of ADHF. Therefore, stratification of risk level according to the score incorporating both clinical factors and biomarkers is clinically relevant, particularly in critically ill patients with multiorgan dysfunctions.

Comparison With NGAL and Other Risk Score

NGAL is a novel biomarker widely utilized to identify AKI patients and detect patients with likely subclinical AKI who have an increased risk of adverse outcomes.[42] A systematic review and meta-analysis[43] demonstrated that the overall c statistic of NGAL to predict AKI is 0.815. This meta-analysis synthesized data from different settings and varied study populations, such as contrast-induced nephropathy, cardiac surgery–associated acute kidney injury. The c statistics of NGAL reported from individual study were less than 0.74, except for 1 study with the c statistic of 0.93,[13] the study population of which was a subgroup of children with an extremely high cutoff point (170 ng/L) and relative small sample size of 119. In contrast, our study has included 507 ADHF adult patients, and the c statistic of NGAL alone as a predictor is only 0.761, much less than that of our risk model (c statistic of 0.874) and risk score (c statistic of 0.859).

Thakar et al[44] reported a risk score using clinical parameters from patients receiving open-heart surgery and yielded an excellent c statistic of 0.81 (95% CI 0.78-0.83). Our score

was developed in a cohort of ADHF patients whose clinical characteristics and risk exposure were different from those of the patients with heart surgery. The c statistic of the proposed score for predicting acute CRS reached 0.859, demonstrating excellent performance of our risk score in ADHF patients.

Sensitivity analysis showed that the 2 incomplete measures had little influence on the risk model. Furthermore, we have kept age, sex, NT-proBNP, and serum albumin in the final risk model, although they were not statistically significant. Age and sex were given factors for controlling potential patients' heterogeneity. NT-proBNP and serum albumin were also found significantly associated with the development of AKI in univariate analysis and by other researchers.[45,46] We also developed a clinical score that reached acceptable performance. Clinicians could choose the one that fits their clinical practice best.

Strengths and Limitations of This Study

Our study has several strengths. First, our risk score was derived for early detection of patients at high risk of developing AKI incorporating, for the first time, both baseline characteristics and novel biomarkers recorded on the first day of admission before a clinically significant change in serum creatinine. Second, the risk score possesses high discriminative power as well as high stability and reproducibility, as shown by concordance between internal and external validation. Third, to develop a prediction tool for early detection of patients who would develop AKI during hospitalization, researchers should exclude those who already have AKI on admission. In our study we excluded those having AKI on admission based on preadmission measurements of serum creatinine, but we did not use this information in developing the risk score; thus, the use of the developed predicting tool is not limited by the need for preadmission serum creatinine. Last, our article closely follows the TRIPOD statement.

The study also has limitations. First, AKI diagnosed by an increase in serum creatinine may introduce the dilemma of using a surrogate outcome to assess the performance of novel models.[47] Evidence of AKI on renal biopsy would be the gold standard but was not feasible in our large cohort. As is the case in most AKI studies, we did not use urine output criteria (ie, <0.5 mL/kg per hour for >6 hours) for AKI diagnosis because urine output as the diagnostic criterion for AKI has been questioned recently for its limited sensitivity when diuretics are administered, reduced specificity in the presence of dehydration, and lack of practicality when an indwelling urinary catheter is not present (as in our setting).[15] Second, our findings remain to be confirmed by other independent studies. The question of whether the model predicts AKI in the special setting of ADHF versus AKI from other causes remains to be addressed. Third, although the study participants were recruited from 6 hospitals located in 5 cities in China, generalizability of the risk score to other populations still needs to be validated. In addition, the bootstrap procedure to estimate the overoptimism was conducted based on the developed risk score, which did not include the model selection step. The estimate of the overoptimism could be substantially biased under this circumstance.

Conclusions

We developed and validated a novel risk score by incorporating both major clinical risk factors and effective urine biomarkers to predict AKI in ADHF patients early. Individual risk prediction, as well as risk stratification based on the risk score, may assist clinicians to assess the risk of AKI in ADHF patients, which, in turn, would help them to plan and initiate the most appropriate disease management for patients in time.

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The authors have followed the STROBE checklist in collecting and reporting their data and the TRIPOD checklist in reporting the prediction model. Elements of the checklist are incorporated into the manuscript. Further details of any particular checklist item are available on request from the corresponding authors.

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Disclosures

None.

References

1. Zhou Q, Zhao C, Xie D, Xu D, Bin J, Chen P, Liang M, Zhang X, Hou F. Acute and acute-on-chronic kidney injury of patients with decompensated heart failure: impact on outcomes. *BMC Nephrol*. 2012;13:51.
2. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J*. 1999;138:285–290.
3. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, Horwitz RI. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. *Am J Cardiol*. 2000;85:1110–1113.
4. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol*. 2004;43:61–67.
5. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. *JAMA*. 2002;287:628–640.

6. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Secular trends in renal dysfunction and outcomes in hospitalized heart failure patients. *J Card Fail*. 2006;12:257–262.
7. Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Young J, Krumholz HM. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail*. 2002;8:136–141.
8. Smith GL, Vaccarino V, Kosiborod M, Lichtman JH, Cheng S, Watnick SG, Krumholz HM. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail*. 2003;9:13–25.
9. Liang KV, Williams AW, Greene EL, Redfield MM. Acute decompensated heart failure and the cardiorenal syndrome. *Crit Care Med*. 2008;36:S75–S88.
10. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, Cotter G, Dittrich H, Massie BM, Dei CL. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. *Eur J Heart Fail*. 2008;10:188–195.
11. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52:1527–1539.
12. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, Haapio M, Hillege H, House AA, Katz N, Maisel A, Mankad S, Zanco P, Mebazaa A, Palazzuoli A, Ronco F, Shaw A, Sheinfeld G, Soni S, Vescovo G, Zamperetti N, Ponikowski P. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J*. 2010;31:703–711.
13. Alvelos M, Pimentel R, Pinho E, Gomes A, Lourenco P, Teles MJ, Almeida P, Guimaraes JT, Bettencourt P. Neutrophil gelatinase-associated lipocalin in the diagnosis of type 1 cardio-renal syndrome in the general ward. *Clin J Am Soc Nephrol*. 2011;6:476–481.
14. Liangos O, Tighiouart H, Perianayagam MC, Kolyada A, Han WK, Wald R, Bonventre JV, Jaber BL. Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. *Biomarkers*. 2009;14:423–431.
15. McCullough PA, Shaw AD, Haase M, Bouchard J, Waikar SS, Siew ED, Murray PT, Mehta RL, Ronco C. Diagnosis of acute kidney injury using functional and injury biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib Nephrol*. 2013;182:13–29.
16. Aghel A, Shrestha K, Mullens W, Borowski A, Tang WH. Serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting worsening renal function in acute decompensated heart failure. *J Card Fail*. 2010;16:49–54.
17. Dupont M, Shrestha K, Singh D, Awad A, Kovach C, Scarcipino M, Maroo AP, Tang WH. Lack of significant renal tubular injury despite acute kidney injury in acute decompensated heart failure. *Eur J Heart Fail*. 2012;14:597–604.
18. Macdonald S, Arendts G, Nagree Y, Xu XF. Neutrophil Gelatinase-Associated Lipocalin (NGAL) predicts renal injury in acute decompensated cardiac failure: a prospective observational study. *BMC Cardiovasc Disord*. 2012;12:8.
19. Maisel AS, Mueller C, Fitzgerald R, Brikhan R, Hiestand BC, Iqbal N, Clopton P, van Veldhuisen DJ. Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: the NGAL EvaLuation Along with B-type NaTriuretic Peptide in acutely decompensated heart failure (GALLANT) trial. *Eur J Heart Fail*. 2011;13:846–851.
20. Shrestha K, Shao Z, Singh D, Dupont M, Tang WH. Relation of systemic and urinary neutrophil gelatinase-associated lipocalin levels to different aspects of impaired renal function in patients with acute decompensated heart failure. *Am J Cardiol*. 2012;110:1329–1335.
21. Verbrugge FH, Dupont M, Shao Z, Shrestha K, Singh D, Finucan M, Mullens W, Tang WH. Novel urinary biomarkers in detecting acute kidney injury, persistent renal impairment, and all-cause mortality following decongestive therapy in acute decompensated heart failure. *J Card Fail*. 2013;19:621–628.
22. Yang X, Chen C, Tian J, Zha Y, Xiong Y, Sun Z, Chen P, Li J, Yang T, Ma C, Liu H, Wang X, Hou FF. Urinary angiotensinogen level predicts AKI in acute decompensated heart failure: a prospective, two-stage study. *J Am Soc Nephrol*. 2015;26:2032–2041.
23. Vaidya VS, Waikar SS, Ferguson MA, Collings FB, Sunderland K, Gioules C, Bradwin G, Matsouaka R, Betensky RA, Curhan GC. Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans. *Clin Transl Sci*. 2008;1:200–208.
24. Nieminen MS, Böhm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, Hasin Y, Lopez-Sendon J, Mebazaa A, Metra M, Rhodes A, Swedberg K, Priori SG, Garcia MAA, Blanc J, Budaj A, Cowie MR, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Garcia MAA, Dickstein K, Albuquerque A, Conthe P, Crespo-Leiro M, Ferrari R, Follath F, Gavazzi A, Janssens U, Komajda M, Morais J, Moreno R, Singer M, Singh S, Tendera M, Thygesen K. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure. *Eur Heart J*. 2005;26:384–416.
25. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AR, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
26. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138.
27. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol*. 1995;48:1503–1510.
28. Harrell FJ, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387.
29. Pencina MJ, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172.
30. Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: the Framingham Study risk score functions. *Stat Med*. 2004;23:1631–1660.
31. Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem*. 2008;54:17–23.
32. Hosmer DWJr, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*. New York: John Wiley & Sons, Inc.; 2013.
33. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ*. 2015;350:g7594.
34. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. *J Am Soc Nephrol*. 2010;21:1757–1764.
35. Yunos N, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012;308:1566–1572.
36. Sarraf M, Masoumi A, Schrier RW. Cardiorenal syndrome in acute decompensated heart failure. *Clin J Am Soc Nephrol*. 2009;4:2013–2026.
37. Katibi KO, Adedoyin OT, Anoba S, Olorunsola BO, Ibrahim OR, Oyeleye AE, Sowunmi FO. Current trends in the management of acute kidney injury in children. *Niger J Paediatr*. 2013;40:314–320.
38. Devarajan P. Emerging biomarkers of acute kidney injury. *Contrib Nephrol*. 2007;156:203.
39. Mehta RL, Cerda J, Burdmann EA, Tonelli M, Garcia-Garcia G, Jha V, Susantitaphong P, Rocco M, Vanholder R, Sever MS, Cruz D, Jaber B, Lameire NH, Lombardi R, Lewington A, Feehally J, Finkelstein F, Levin N, Pannu N, Thomas B, Aronoff-Spencer E, Remuzzi G. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet*. 2015;385:2616–2643.
40. Matsui K, Kamijo-Ikemori A, Sugaya T, Yasuda T, Kimura K. Usefulness of urinary biomarkers in early detection of acute kidney injury after cardiac surgery in adults. *Circ J*. 2011;76:213–220.
41. Molitoris BA, Melnikov VY, Okusa MD, Himmelfarb J. Technology Insight: biomarker development in acute kidney injury—what can we anticipate? *Nat Clin Pract Nephrol*. 2008;4:154–165.
42. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, Krawczeski CD, Koyner JL, Murray P, Zappitelli M, Goldstein SL, Makris K, Ronco C, Martensson J, Martling CR, Venge P, Siew E, Ware LB, Ikizler TA, Mertens PR. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. *J Am Coll Cardiol*. 2011;57:1752–1761.
43. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis*. 2009;54:1012–1024.
44. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol*. 2005;16:162–168.
45. Valdespino-Trejo A, Orea-Tejeda A, Castillo-Martinez L, Keirns-Davis C, Montanez-Orozco A, Ortiz-Suarez G, Delgado-Perez DA, Marquez-Zepeda B. Low albumin levels and high impedance ratio as risk factors for worsening kidney function during hospitalization of decompensated heart failure patients. *Exp Clin Cardiol*. 2013;18:113–117.
46. Pfister R, Müller Ehmsen J, Hagemeister J, Hellmich M, Erdmann E, Schneider CA. NT-pro-BNP predicts worsening renal function in patients with chronic systolic heart failure. *Intern Med J*. 2011;41:467–472.
47. McIlroy DR, Wagener G, Lee HT. Neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery: the effect of baseline renal function on diagnostic performance. *Clin J Am Soc Nephrol*. 2010;5:211–219.

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Study Design. The study is a prospective, multi-center, observational study. All patients provided informed written consent for the procedure(s) and the study was approved by the Institutional Review Board.

Study Population. A total of 676 consecutive participants, aged 18-80 years old, were prospectively enrolled between September 2011 and August 2014 from six regional central hospitals located in five cities in China. Among the participants, 169 were excluded according to exclusion criteria (Figure 1), and the remaining 507 participants formed our study population.

The inclusion criteria were patients with ADHF 1) who were admitted to the six participating hospitals, and 2) who had at least three measurements of serum creatinine over a six-month period before admission. Exclusion criteria were 1) exposing to nephrotoxins, such as contrast media, aminoglycoside antibiotics, vancomycin, and/or non-steroidal anti-inflammatory drugs except aspirin, within 4 weeks before admission or during hospital stay, 2) pre-existing advanced chronic kidney disease (CKD) (chronic dialysis or pre-admission estimated glomerular filtration rate [Egfr] <30 ml/min/1·73m^2), 3) urinary tract infection or obstruction, cancer, a concurrent diagnosis of an acute coronary syndrome, cardiogenic shock or need for inotropes, 4) heart failure following cardiac surgery, and 5) having AKI on admission (i.e., those with a 50% increase in serum creatinine from preadmission level on the day of hospitalization).

Laboratory measurements

Urine and blood samples were measured in a central laboratory with standard protocol. A sandwich ELISA kit (Immuno-Biologic Laboratories Co. Ltd, Japan) was used for

quantifying AGT in urine, and further confirmed by western blot analyses. uNGAL was measured with an ELISA kit (Antibody Shop, Denmark). Urine albumin to creatinine ratio (UACR) was measured using an automatic analyzer (Siemens BNPro Spec, Germany). All urine biomarkers were normalized based on the level of urinary creatinine. Estimated glomerular filtration rate (GRF) was determined by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (1).

Candidate predictors

Candidate predictors included clinical variables such as sex, age (years), hypertension, diabetes mellitus, pre-existing CKD indicated from medical records, or reported by patients, or diagnosed by doctor, prior hospitalization for heart failure, left ventricular ejection fraction, severity of breathlessness by the New York Heart Association (NYHA) classification, NT-proBNP (pg/ml), systolic and diastolic blood pressure (mmHg), serum albumin (g/L), serum creatinine (μmol/L), hemoglobin (g/L), use of renin-angiotensin system blockersand/or diuretic, and urine biomarkers such as urine albumin to creatinine ratio (UACR, mg/g Cr), uNGAL (μg/g Cr) and uAGT (μg/g Cr). All these variables were assessed and recorded on admission.

Statistical analysis

We took two steps to develop a risk model based on the development cohort. The first was to select meaningful clinical risk factors (non-urine markers) by logistic regression with backward elimination. Clinical candidate predictors significant at $P<0.1$ in univariate logistic regression models were considered for backward elimination. In this step, a clinical model with clinical factors was developed. Then, urine biomarkers (UACR, uNGAL and uAGT) were evaluated sequentially based on this clinical model. The likelihood ratio χ^2 test (2) was used to evaluate the significance of the added urine biomarkers, and net-reclassification index

(NRI) and integrated discrimination improvement (IDI) (3) were used to quantify the additional contribution of these urine biomarkers to risk reclassification.

To develop the risk score, the scoring method similar to Sullivan *et al*'s (4) was employed based on the developed risk model. Continuous variables were divided into categories in terms of clinical significance except for NT-proBNP, for which the cut-off of 5578 pg/ml was chosen to yield good sensitivity and specificity. Mid-point value was defined as the reference value of each category. For the first and last categories of each variable, we used the 1^{st} and the 99^{th} percentiles to minimize the influence of extreme values. For each risk factor, the lowest risk category was chosen as the base category, and the distance of other categories from the base category was calculated as the difference of reference values between corresponding categories and base category multiplied by the regression coefficient of corresponding variable in the generated risk model. One point of the risk score system was defined as a constant of 0.141 which means the increase of risk associated with a 10-year increase in age, that is 0.0141×10. The score of each base category was set at 0, and that of other categories were computed by dividing corresponding distance from the base category by the constant of 0.141 and then rounded to the nearest integer. The total risk score for an individual patient is obtained by summing up the score of each predictive variable.

The predictive accuracy of the risk model and the risk score model was assessed by both discrimination measured by *C*-statistic (5) and calibration evaluated by Hosmer-Lemeshow χ^2 statistic (6) and calibration plot, a plot of observed proportions versus predicted probabilities. Bootstrapping technique (7) was used to adjust for over-fitting and over-optimistic model performance.

The natural logarithmic transformation of NT-proBNP and all urine biomarkers was made because of their extreme positive skewness. Generalized additive model (GAM) (8) was used to explore the potential nonlinear relationship between those continuous variables

and the outcome. The clinical meaningful interactions between predictors were also examined. Continuous variables were expressed as mean (SD) or median (1^{st} Quarter-3^{rd} Quarter). Categorical variables were expressed as percentages. Sensitivity analysis was conducted to assess the influence of the two incomplete measures by leaving the corresponding two cases out. Further, we also applied the risk score to the whole participants as sensitivity analysis. All analyses were done with SAS (SAS Institute Inc., Cary, NC, version 9.4). A two-sided $P<0.05$ was considered statistically significant.

Table S1: Baseline characteristics outlining those who developed versus not developed AKI.

Values are numbers (percentages) unless stated otherwise.

	Non-AKI (n=339)	AKI (n=168)	P value
Demographics			
mean (SD) age (years)	63.0(15.3)	69.6(13.1)	<.001
Sex, Male	211(62.2)	109(64.9)	0.562
Pre-existing clinical conditions			
Hypertension	146(43.1)	107(63.7)	<.001
Diabetes	68(20.1)	61(36.3)	<.001
Pre-CKD	55(16.2)	78(46.4)	<.001
Prior hospitalization for HF	170(50.1)	91(54.2)	0.394
Primary causes of heart failure			
Ischemic heart disease	178(52.5)	93(55.4)	0.545
Hypertension	43(12.7)	22(13.1)	0.896
Rheumatic heart disease	47(13.9)	23(13.7)	0.957
Cardiomyopathy	48(14.2)	14(8.3)	0.059
Other	23(6.8)	16(9.5)	0.276
Characteristics on admission			
LVEF<45%	153(45.1)	81(48.2)	0.512
NYHA, class IV	144(42.5)	99(58.9)	<.001
Median (IQR) NT-proBNP (pg/ml)	4181.0(1942.0-8463.0)	7088.5(3699.3-9000.0)	<.001
Mean (SD) SBP (mmHg)	126.2(24.0)	129.3(24.8)	0.173
Mean (SD) DBP (mmHg)	75.6(16.1)	74.8(14.4)	0.591
Mean (SD) Serum creatinine (μmol/L)	98.5(40.0)	128.8(59.1)	<.001
Mean (SD) Serum albumin (g/L)	34.8(5.8)	30.8(5.9)	<.001
Mean (SD) Hemoglobin (g/L)	128.1(23.1)	115.8(26.3)	<.001
Treatment before Admission			
Use ACEI/ARB pre-admission	90(26.5)	54(32.1)	0.189
Mean (SD) Drug index of ACEI/ARBc	4.3(1.1)	4.1(1.2)	0.283
Use spironolactone	103(30.4)	60(35.7)	0.226
Mean (SD) Drug index of spironolactonec	1.1(0.3)	1.1(0.3)	0.314
Mean (SD) Drug score of RAAS blockerc	5.4(1.1)	5.2(1.4)	0.476
Use diuretic pre-admission	117(34.5)	66(39.3)	0.292
Use of high-dose diuretic	5(1.5)	5(3.0)	0.253
Biomarker measurement			
Median (IQR) UACR (mg/g Cr)	51.2(16.2-182.4)	180.4(63.7-491.5)	0.012
Median (IQR) uNGAL (μg/g Cr)	29.7(14.9-78.3)	114.2(39.1-417.2)	<.001

Median (IQR) uAGT (μg/g Cr)	21.0(5.7-51.4)	162.7(56.0-393.6)	<.001

Abbreviations: IQR, interquartile Range; AKI, Acute Kidney Injury; pre-CKD, pre-existing chronic kidney disease; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; UACR, urine albumin to creatinine ratio. uNGAL, urinary neutrophil gelatinase-associated lipocalin; uAGT, urinary angiotensionogen.

* Defined as pre-admission eGFR<60ml/min/1.73m2. Pre-admission eGFR=the mean of at least three measurements over a six-month period before admission

Table S2. C-statistic, NRI and IDI for different models

Models	VS	$LR\,\chi^2$	*P*	C-statistic(95%CI)	NRI	IDI
Clinical model (M1)*				0.767(0.714-0.820)		
M1 + uAGT (M2)	M1	64.923	<0.001	0.861(0.820-0.925)[#]	0.809 （p<0.001）	0.169 （p<0.001）
M1 +uAGT+ uNGAL (M3)	M2	8.737	<0.013	0.874(0.835-0.913)[#&]	0.293 （p=0.012）	0.023 （p=0.011）
M1 +uAGT+ uNGAL+UACR (M4)	M3	1.582	0.208	0.875(0.836-0.914)	0.105 (p=0.369)	0.004 (p=0.214)

***** Clinical model included age, sex, pre-existing CKD, ALB and NT-proBNP.

[#] VS M1, DeLong's test, $P < 0.001$

[#] VS M2, DeLong's test, $P = 0.035$

Table S3. Predicted risk of AKI in patients with ADHF based on the risk score model.

Total risk score	Predicted risk (%)	Total risk score	Predicted risk (%)	Total risk score	Predicted risk (%)
0	1.8	19	13.7	38	58.5
1	2.0	20	15.1	39	61.3
2	2.2	21	16.6	40	63.9
3	2.5	22	18.3	41	66.6
4	2.7	23	20.1	42	69.1
5	3.1	24	22.0	43	71.5
6	3.4	25	24.0	44	73.7
7	3.8	26	26.2	45	75.9
8	4.3	27	28.5	46	78.0
9	4.8	28	30.9	47	79.9
10	5.3	29	33.4	48	81.7
11	5.9	30	36.0	49	83.3
12	6.6	31	38.7	50	84.9
13	7.4	32	41.4	51	86.3
14	8.2	33	44.2	52	87.6
15	9.1	34	47.1	53	88.8
16	10.1	35	50.0	54	89.9
17	11.2	36	52.8	55	90.9
18	12.4	37	55.7		

Table S4. Risk score for single risk factors associated with developing AKI for clinical score model in ADHF patients.

Risk Factor	Score	C-statistic for single variable
Age (year)		0.638 (0.574-0.701)
≤55	0	
56-65	2	
66-75	3	
76 and older	5	
Sex		0.514 (0.460-0.568)
Male	1	
Female	0	
Pre-CKD		0.680 (0.627-0.732)
Yes	5	
No	0	
Serum albumin (mmol/L)		0.640 (0.576-0.704)
≤35	4	
>35	0	
NT-proBNP (pg/ml) †		0.635 (0.572-0.698)
＜5578	0	
≥5578	3	

Table S5. Sensitivity analysis of model performance of models with different included variables.

Included variables	Development dataset			Validation dataset
	-2 Log L	AIC	C-statistic	C-statistic
Age / Sex / pre-CKD / ln-NT-proBNP / Serum albumin	345.736	357.736	0.767	0.807
Age / Sex / pre-CKD / ln-NT-proBNP / Serum albumin / ln-uNGAL	314.196	328.196	0.819	0.823
Age / Sex / pre-CKD / ln-NT-proBNP / Serum albumin / ln-uAGT	280.813	294.813	0.861	0.888
Age / Sex / pre-CKD / ln-NT-proBNP / Serum albumin / ln-uNGAL / ln-uAGT	272.076	288.076	0.874	0.890
Age / Sex / eGFR / ln-NT-proBNP / Serum albumin	355.295	367.295	0.751	0.825
Age / Sex / eGFR / ln-NT-proBNP / Serum albumin / ln-uNGAL	320.421	334.421	0.812	0.841
Age / Sex / eGFR / ln-NT-proBNP / Serum albumin / ln-uAGT	288.065	302.065	0.854	0.898
Age / Sex / eGFR / ln-NT-proBNP / Serum albumin / ln-uNGAL / ln-uAGT	277.847	293.847	0.867	0.903

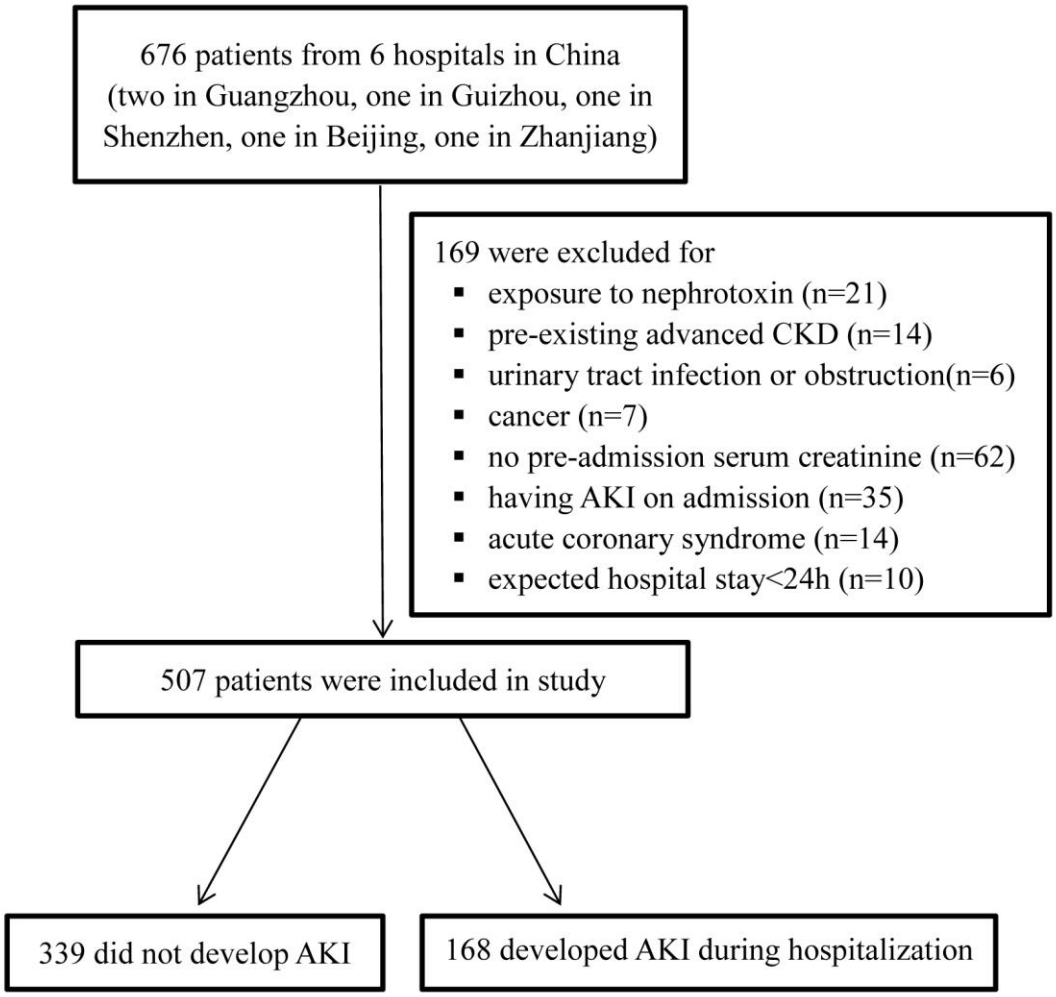

Figure S1. Flow of enrollment of the study participants.

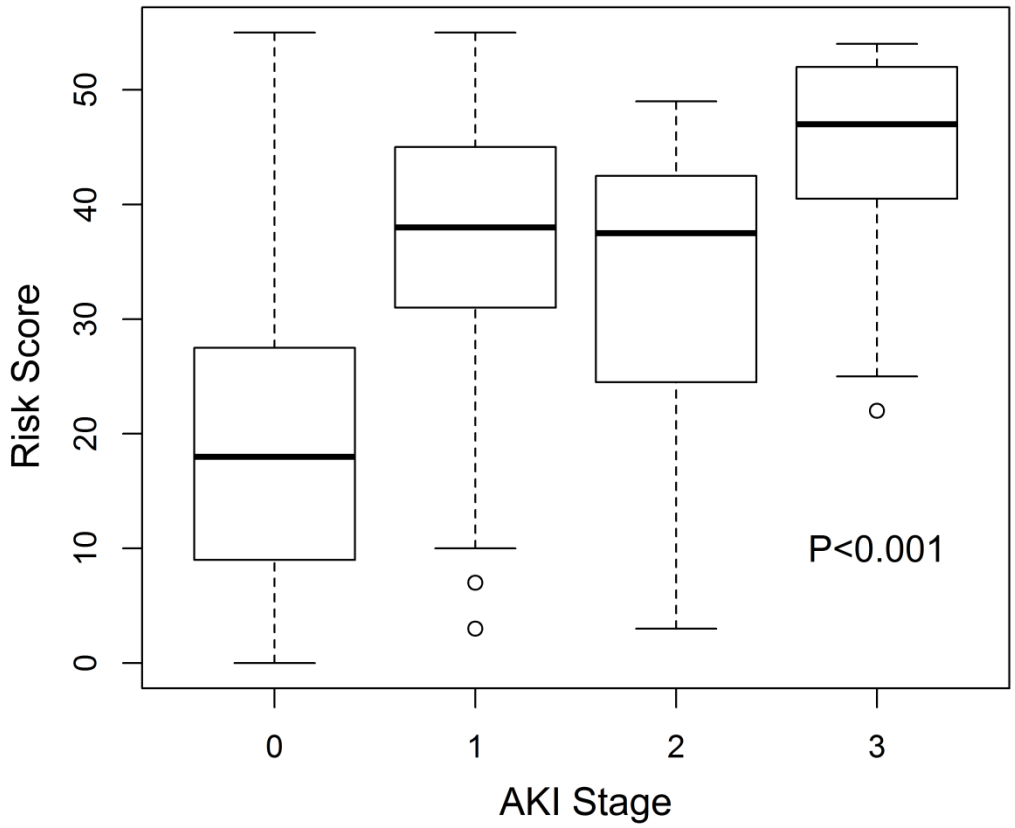

Figure S2. Boxplot showing the risk score across different AKI stage of the patients. Significant difference in average risk score of different AKI stage was found, with higher risk score in patients with higher stage of AKI (P value by one-way ANOVA analysis, <0.001).

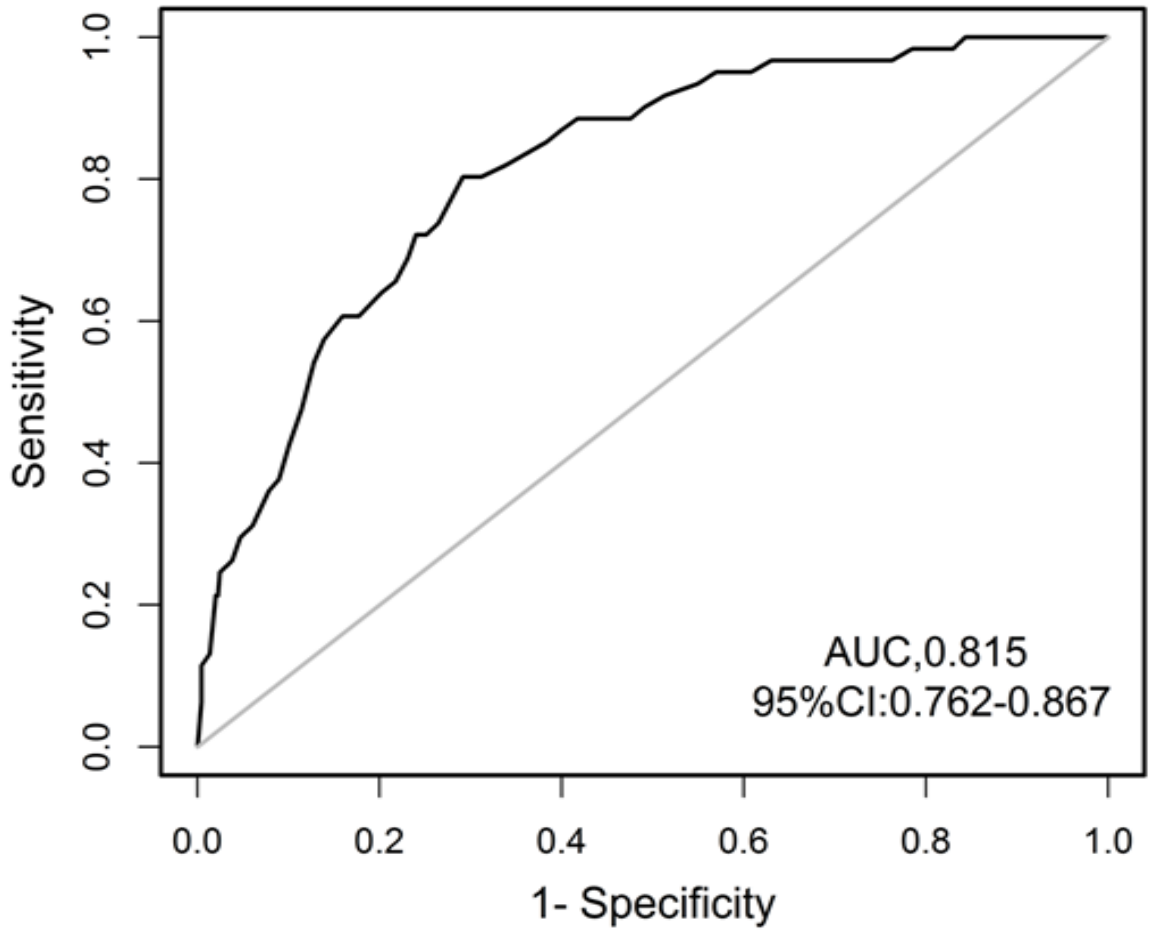

Figure S3. Receiver Operator Characteristic Curves showing the discriminatory power of the risk score for predicting death during hospitalization.

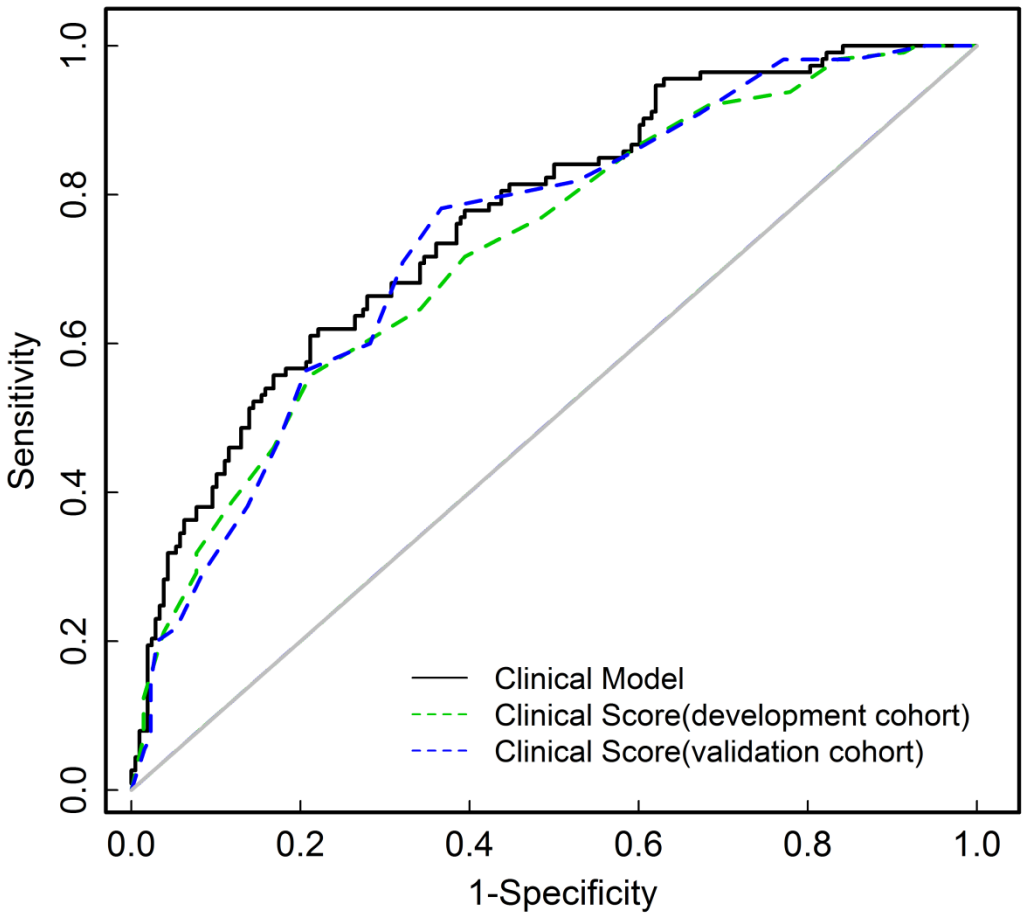

Figure S4. Receiver Operator Characteristic Curves showing Area Under the Curve of clinical model and clinical score for AKI in ADHF patients.

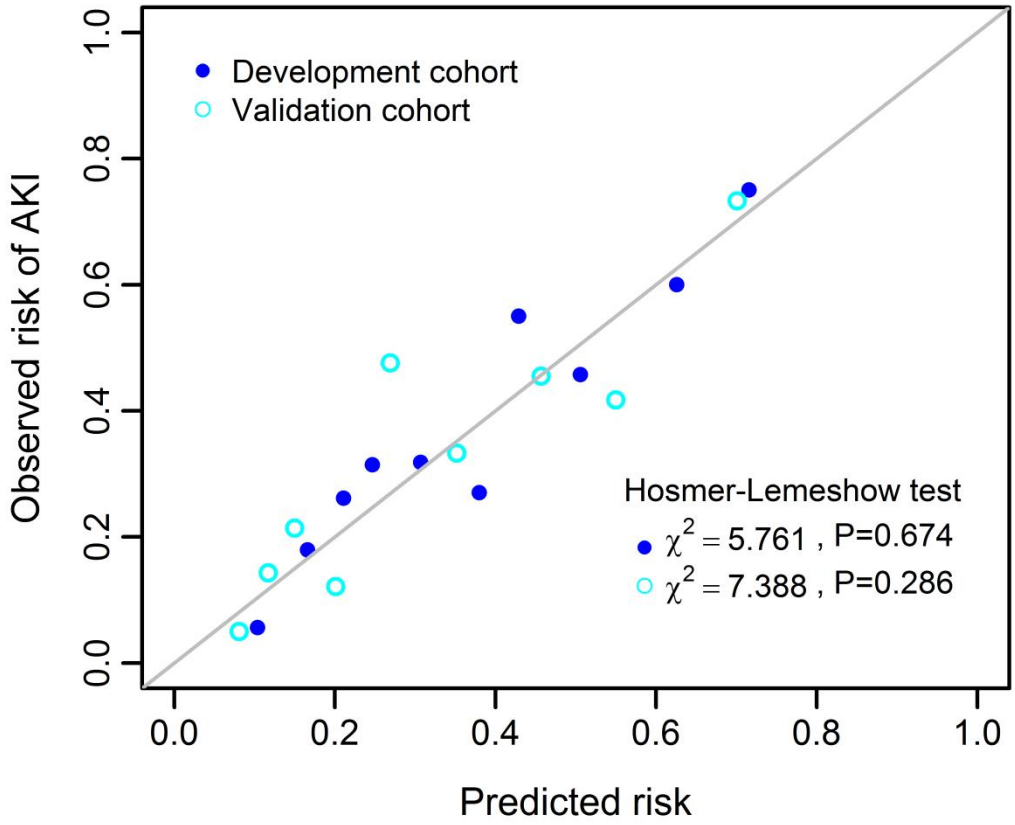

Figure S5. Calibration plot as well as the Hosmer- Lemeshow χ^2 statistic for the risk score in both development and validation cohorts. The points and circles indicate the observed frequencies by decile of predicted probability.

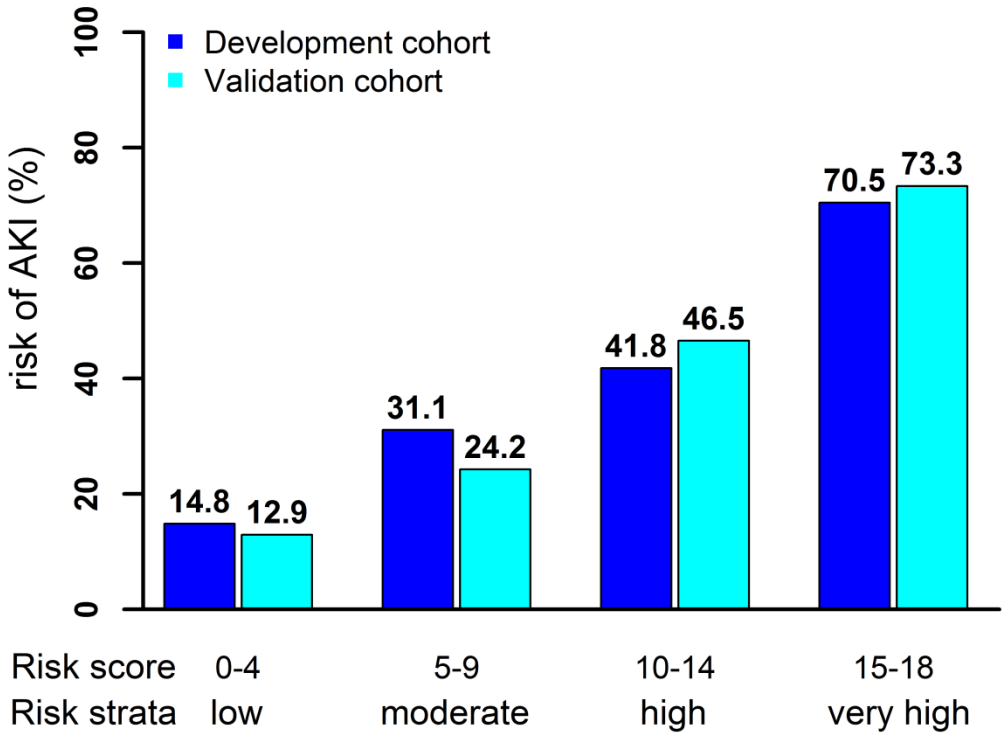

Figure S6. Risk levels according to the risk score in development and validation cohorts. Risks were categorized into low-risk (0-4 points), moderate-risk (5-9 points), high-risk (10-14 points), very high-risk (15-18 points). Higher points means higher risk of developing AKI in patients with ADHF, *P* for trend<0.001.

Supplemental risk calculator AKI risk calculator**.**

Supplemental References:

1. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AR, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009; 150:604-612.

2. Tabachnick BG, Fidell LS, Osterlind SJ. Using multivariate statistics. 2001.

3. Pencina MJ, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med.* 2008; 27:157-172.

4. Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: the Framingham Study risk score functions. *Stat Med.* 2004; 23:1631-1660.

5. Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem.* 2008; 54:17-23.

6. Hosmer Jr DW, Lemeshow S, Sturdivant RX. *Applied logistic regression*: Wiley.com; 2013.

7. Efron B, Tibshirani RJ. *An introduction to the bootstrap*: CRC press; 1994.

8. Hastie TJ, Tibshirani RJ. *Generalized additive models*: CRC Press; 1990.