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A LASSO-derived clinical score to predict severe acute kidney injury in the cardiac surgery recovery unit: a large retrospective cohort study

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Abstract

Objectives We aimed to develop an effective tool for predicting severe acute kidney injury (AKI) in patients admitted to the cardiac surgery recovery unit (CSRU).

Design A retrospective cohort study.

Setting Data were extracted from the Medical Information Mart for Intensive Care (MIMIC)-III database, consisting of critically ill participants between 2001 and 2012 in the USA.

Participants A total of 6271 patients admitted to the CSRU were enrolled from the MIMIC-III database.

Primary and secondary outcome Stage 2 to 3 AKI.

Result As identified by least absolute shrinkage and selection operator (LASSO) and logistic regression, risk factors for AKI included age, sex, weight, respiratory rate, systolic blood pressure, diastolic blood pressure, central venous pressure, urine output, partial pressure of oxygen, sedative use, furosemide use, atrial fibrillation, congestive heart failure, and left heart catheterization, all of which were used to establish a clinical score. The areas under the receiver operating characteristic curve of the model were 0.779 for the primary cohort and 0.778 for the validation cohort. The calibration curves showed good agreement between the predictions and observations. Decision curve analysis demonstrated that the model could achieve a net benefit.

Conclusion A clinical score built by using LASSO regression and logistic regression to screen multiple clinical risk factors was established to estimate the probability of severe AKI in CSRU patients. This may be a portable and practical tool for severe AKI prediction in the CSRU.

Key words: acute kidney injury, LASSO, clinical score, cardiac surgery recovery unit, prediction

Strengths and limitations of this study

This is the first study to develop and validate a prognostic clinical score for predicting severe AKI in CSRU patients.

The performance of this novel nomogram model in both the primary cohort and validation cohort was evaluated with the area under the receiver operating characteristic curve, calibration curves, decision curve analysis and survival curves.

Because only patients without existing renal failure were included in this study, this novel nomogram model might not be suitable for those with a renal failure history.

We did not compare the performance of the nomogram model with that of existing models.

Introduction

Acute kidney injury (AKI), a common complication in patients admitted to the intensive care unit worldwide[1 2], is associated with adverse short- and long-term prognoses[3]. It has been reported that more than half of patients in the cardiac surgery recovery unit (CSRU) suffer from AKI of some stage[4], which is associated with high mortality and rehospitalization rates[5]. Early rapid diagnosis and treatment of AKI may help reduce mortality and rehospitalization rates. Although several biomarkers have been used for early diagnostic and prognostic prediction of AKI[6 7], the clinical utilization of these biomarkers has been limited. When the levels of these biomarkers increase, renal injury occurs. Thus, identifying critically ill patients at high risk of AKI is an important part of the overall management of CSRU patients.

A nomogram is a popular graphical calculation device that incorporates possible risk factors to make clinical prognostic predictions, which are presented as a scale or score. It has been

extensively used to predict oncological prognosis[8]. Recently, researchers established a nomogram for forecasting the occurrence of AKI in patients undergoing cardiac surgery[9]. However, their small, single-center study did not exclude patients with chronic kidney disease, so it probably overestimated the occurrence of AKI; additionally, only logistic regression for variable selection was used. While least absolute shrinkage and selection operator (LASSO) regression is of great strength for variable selection because it can efficiently address the potential association between covariates, such as collinearity[10].

Accordingly, in this study, we performed LASSO regression to select variables and built a logistic regression model to identify independent risk factors for severe AKI in patients admitted to the CSRU. We aimed to determine the risk factors for severe AKI and develop a clinical score for evaluating the probability that patients undergoing critical cardiac care will acquire severe AKI.

Method

Data source and ethics approval

The data were extracted from the Medical Information Mart for Intensive Care (MIMIC)-III dataset. As a large and publicly available database, MIMIC-III comprises the clinical information for 61532 ICU stay cases between 2001 and 2012. The use of the MIMIC-III database was approved by the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center[11]. Since the information used in the study was from a publicly deidentified database, informed consent was waived.

Study population

Adult ICU stays longer than 1 day were included. When a patient had multiple ICU admissions, only the first medical record was selected in the study. The exclusion criteria were as follows: patients in units other than the CSRU (n = 24074, 77.8%), patients with no urine output records (n = 105, 0.3%), patients with no creatinine data (n = 439, 1.4%), and patients with existing renal failure (n = 39, 0.1%) (Figure 1). During the CSRU stay, all creatinine and urine output records were extracted and AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[12]. In this study, severe AKI was defined as stage 2 or stage 3 AKI under the KDIGO criteria. Patients in the CSRU were screened, and a total of 6271 patients were included. Chronologically, the first 70% of patients were allocated to the primary cohort, and the last 30% were allocated to the validation cohort. Subsequently, we established a clinical score model by using the primary cohort data and validated the model by using the validation cohort.

Variables extraction

The following variables were extracted.

Demographics: age (years), sex, height (cm), and weight (kg).

Vital signs: heart rate (/min), respiratory rate (/min), temperature (℃), saturation of peripheral oxygen (%), blood glucose level (mg/dL), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), central venous pressure (CVP, mmHg), and mean artery pressure (mmHg). The mean value of vital signs in the 24 hours after admission was enrolled for analysis.

Laboratory tests: white blood cell count (×10^9/L), hemoglobin (g/dL), platelets (×10^9/L), chloride (mmol/L), sodium (mmol/L), blood urea nitrogen (BUN, mg/dL), bicarbonate (mmol/L), pH, partial pressure of oxygen (pO_2, mmHg), partial pressure of carbon dioxide (pCO_2, mmHg), creatinine (md/dL), and potassium (mmol/L). The values of laboratory tests in the first 24 hours after admission were used for the analysis. In addition, 24-hour urine output was extracted.

Procedures: administration of furosemide, use of sedative, ventilation, vasopressor, cardiopulmonary bypass, coronary artery bypass grafting, left heart catheterization. The sedative drugs in this study included midazolam, fentanyl, propofol, and midazolam.

Comorbidities: coronary artery disease, congestive heart failure, atrial fibrillation, stroke, diabetes, renal disease, liver disease, chronic obstructive pulmonary disease, and malignancy.

All the variables were collected in the initial 24 hours after admission aiming to predict severe AKI as early as possible. The frequency of missing values of each variable was less than 15%. The missing values were filled in by the random forest method using R software.

Statistical analysis

Continuous variables are denoted as the mean ± SD or the median (interquartile range), whereas categorical variables are expressed as number (percentage). Continuous data were compared with Student's t-test or the rank-sum test, while categorical data were compared using the chi-square test.

In this study, LASSO was performed for variable selection. LASSO regression is a compression estimation used to address the collinearity between covariates. When there are

several collinear predictors, LASSO selects only one and ignores the others or zeroes out some regression coefficients. Odds ratios (ORs) with 95% confidence intervals (95% CIs), statistics describing the strength of the association between disease and exposure, were calculated by logistic regression, thus estimating the association of independent risk factors with AKI. Finally, a clinical score model was established based on the above analysis, which was further validated with C-indices, receiver operating characteristic (ROC) curves, the areas under the ROC curves (AUCs), calibration curves, and decision curve analysis.

SPSS software (version 23.0, IBM, New York, USA) and R software (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. A two-sided $P<0.05$ was considered statistically significant.

Patient and public involvement

Patients and/or the public were not directly involved in this study.

Results

Patients with severe AKI comprised 55.9% (2452/4388) and 54.2% (1020/1883) of the primary and validation cohorts, respectively. No significant difference in the severe AKI rate was observed between the two cohorts ($P=0.213$). Except for SBP (primary cohort 113.3 mmHg vs. validation cohort 132.4 mmHg, $P=0.040$), no clinical characteristics showed a significant difference between the primary and validation cohorts (Table 1).

In the primary cohort, patients with severe AKI were older, had higher weights and had higher levels of blood glucose than those without severe AKI ($P < 0.001$). SBP and DBP were

significantly lower (112.7 mmHg vs. 114.0 mmHg and 56.6 mmHg vs. 57.9 mmHg) while CVP was significantly higher (11.2 mmHg vs. 9.8 mmHg) in the severe AKI group (P<0.001). Urine output and pO_2 were lower in the severe AKI group (P < 0.01). Drug administration was also different, namely, severe AKI patients received sedatives, ventilation, and furosemide significantly more often (P<0.001). The stroke prevalences were the same, but a higher prevalence of atrial fibrillation, congestive heart failure and left heart catheterization was observed in severe AKI patients (P<0.05) (Table 2).

To confirm the possible risk factors for severe AKI, we performed LASSO regression to select variables. A total of 18 variables were enrolled for further analysis according to the 1 − standard error criteria (Figure 2). Then we conducted logistic regression analysis based on the LASSO results. Age (OR: 1.017, 95% CI: 1.010-1.023), male sex (OR: 0.667, 95% CI: 0.568-0.7844), weight (OR: 1.032, 95% CI: 1.027-1.037), respiratory rate (OR: 0.959, 95% CI: 0.936-0.982), SBP (OR: 0.990, 95% CI: 0.983-0.997), DBP (OR: 0.985, 95% CI: 0.974-0.997), CVP (OR: 1.075, 95% CI: 1.051-1.099), urine output (OR: 0.999, 95% CI: 0.999-0.999), pO_2 (OR: 0.999, 95% CI: 0.998-1.000), sedative use (OR: 1.405, 95% CI: 1.032-1.912), use of furosemide (OR: 0.469, 95% CI: 0.387-0.569), atrial fibrillation (OR: 1.322, 95% CI: 1.139-1.536), congestive heart failure (OR: 1.357, 95% CI: 1.143-1.611), and left heart catheterization (OR: 1.181, 95% CI: 1.014-1.376) were associated with severe AKI (Table 3).

Next, we included the above significant factors to build a clinical score based on the logistic regression model (Figure 3). Each level of every variable was assigned a score. By adding the scores for all of the selected variables, the total score was obtained. By checking the number corresponding to the total scores, the probability of severe AKI can be estimated for a given

patient. Another nomogram version with scales instead of numbers is supplied as well (Supplementary Figure 1).

The C-indices were 0.779 for the primary cohort and 0.778 for the validation cohort. The ROC curves demonstrated that the model had good discriminative ability in both the primary cohort (AUC: 0.779, 95% CI: 0.766-0.793) and the validation cohort (AUC: 0.778, 95% CI: 0.757-0.799). Calibration plots showed that the apparent curves were adjacent to the ideal curves in both the primary and validation groups. Finally, decision curve analysis was performed to compare the clinical usability and benefits of the model. The decision curves showed acceptable net benefits across a range of high risks of severe AKI in the primary and validation cohorts (Figure 4).

We also evaluated the model performance after excluding the variable of urine output. Without urine output information, the model also showed acceptable discriminative ability in both the primary cohort (AUC: 0.713, 95% CI: 0.698-0.728) and the validation cohort (AUC: 0.718, 95% CI: 0.695-0.741) (Supplementary Figure 2).

Discussion

AKI is a complicated clinical syndrome characterized by reduced urine production and/or rapid increases in serum creatinine[13]. AKI has been reported to be positively associated with short-term mortality in CSRU populations[5 14]. Delayed diagnosis of AKI is an independent risk factor for nosocomial death[15]. Therefore, early identification of patients at risk for AKI might help to reduce short-term mortality, improve prognosis, and reduce the health care burden.

In this study, we extracted the clinical information for 6271 patients from the MIMIC-III

database. We identified the following 14 possible risk factors for severe AKI by LASSO regression and logistical regression: age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO_2, sedative use, furosemide, atrial fibrillation, congestive heart failure, and left heart catheterization. Subsequently, a clinical score model was constructed by quantifying the weight of the aforementioned variables. The clinical score model was well fitted, as evaluated by the AUC, calibration curves and decision curve analysis in both the primary and validation cohorts. The model could calculate a severe AKI probability immediately after the initial 24 hours and might help clinicians perform early intervention.

Several scoring systems and prognostic models have been built to predict AKI. Scoring systems such as the Cleveland Clinic Score[16] and the Mehta Score[17] only consider AKI patients requiring dialysis, so they might miss patients with subclinical AKI. Additionally, nomograms have been used to forecast AKI in patients undergoing cardiac surgery[9] or coronary angiography[18]. These studies enrolled both mild and severe AKI patients. Our model was generated from the MIMIC-III database, with a larger sample size and more variables. This study predicted only severe AKI, which might be more attractive for clinical practice. Moreover, the primary cohort and validation cohort were assigned by admission time. According to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement, nonrandom assignment by time is a stronger design feature for evaluating model performance than random assignment[19].

LASSO regression is a popular variable selection algorithm for multicollinear data or high-dimensional data[20]. LASSO has been widely used for clinical prediction. For example, via LASSO, researchers have built a nomogram to predict the diagnosis and prognosis of colon

cancer[21]. A radiomics signature using LASSO has been developed to evaluate survival in patients with non-small-cell lung cancer[22]. LASSO has been used to predict AKI in patients with hematologic tumors, patients suffering from cardiac surgery or patients hospitalized in the neurosurgical intensive care unit[10 20 23]. In the present study, based on clinical profiles, LASSO was performed to select relevant coefficients from a multitude of variables, simultaneously removing all unrelated variables. Through dimensionality reduction using LASSO, 42 clinical variables were screened down to 14 risk factors, according to the 1 − standard error criteria.

Among those 14 variables, older age and obesity were independent risk factors for AKI, as indicated by previous investigations[24 25]. Additionally, hypotension has been reported to be associated with new-onset AKI in ICU patients with shock[26]. High CVP, indicating fluid overload, was another factor affecting AKI[27]. Consistent with previous studies, these risk factors were included in the nomogram and given a weighted score. Reduced urine output is a clinical manifestation of AKI and is also an important factor underlying the poor prognosis of AKI. In this study, decreased urine output was one of the most important predictors of AKI in CSRU patients. Overall, the nomogram contained 14 variables, more than half of which have been reported to be associated with AKI. In addition, ROC curves, calibration curves, and decision curve analysis showed consistent results in both the primary and validation cohorts, showing that the clinical score model could be an effective and reliable tool for predicting the risk of severe AKI.

Several limitations of our study must be noted. First, this study was based on the MIMIC-III database, whose data were collected between 2001 and 2012. Some therapies might not meet the latest guidelines and some newer medicines might not be covered here. Because of the

single-center nature of the data, the performance of our model might be influenced when applied to other regions. The potential residual confounding by variables not recorded in this database could not be evaluated. Second, only patients without existing renal failure were included in this study. Thus, this novel nomogram model might not be suitable for those with a renal failure history. Third, missing values were filled by the random forest method, which might lead to biased regression coefficient estimates[28]. Therefore, further studies are needed to verify our model. Fourth, our model was designed to be used immediately after the initial 24 hours of admission, and it could not work for patients who suffer AKI within those initial 24 hours.

Conclusion

In conclusion, this study established and validated a novel clinical score by using LASSO regression and logistic regression to screen for multiple clinical risk factors to estimate the probability of severe AKI in CSRU patients. This clinical score model can be a portable and reliable predictive tool that might help in individualized clinical decision-making and risk management for severe AKI.

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and data interpretation. JH: Data collection and data curation. JH: Data collection and data curation. YZ: Literature search and data interpretation. QG: Conceptualization, writing review and editing, and data curation. JW: Conceptualization, writing review and editing, and data curation.

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Table 1 Baseline characteristics of the enrolled subjects in the primary and validation cohorts.

	Primary cohort	Validation cohort	*P*
n	4388	1883	
Age, years	66.0±12.8	65.9±13.3	0.715
Male	2921 (66.6)	1229 (65.3)	0.332
Weight, kg	83.0±19.1	83.2±20.0	0.785
Heart rate, /min	84.9±10.7	84.6±10.8	0.357
Respiratory rate, /min	17.2±3.1	17.2±3.0	0.914
Glucose, mg/dL	131.2±23.2	132.4±23.2	0.060
SBP, mmHg	113.3±10.7	113.9±10.8	0.040
DBP, mmHg	57.1±6.9	57.3±7.0	0.244
CVP, mmHg	10.6±3.5	10.7±3.6	0.191
Urine output, mL	2075.0 (1480.0-2880.0)	2080.0 (1457.0-2900.0)	0.949
pO_2, mmHg	314.0 (211.0-383.0)	308.0 (206.0-386.0)	0.168
Sedative	3707 (84.5)	1593 (84.6)	0.905
Ventilation	3836 (87.4)	1642 (87.2)	0.811
Furosemide	675 (15.4)	292 (15.5)	0.901
Atrial fibrillation	1695 (38.6)	754 (40.0)	0.293
Congestive heart failure	1018 (23.2)	442 (23.5)	0.814
Stroke	258 (5.9)	108 (5.7)	0.823
Left heart catheterization	1288 (29.4)	551 (29.3)	0.942
Severe AKI	2452 (55.9)	1020 (54.2)	0.213

Data are depicted as the mean ± standard deviation, the median (interquartile range) or a number (percentage). Continuous data were compared with Student's t test or the rank-sum test, while categorical data were compared using the chi-square test. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; pO_2, partial pressure of oxygen; AKI, acute kidney injury.

Table 2 Baseline characteristics of the severe AKI and nonsevere AKI groups in the primary cohort.

	Severe AKI	Non-severe AKI	*P*
n	2452	1936	
Age, years	67.4±12.2	64.3±13.3	<0.001
Male	1606 (65.5)	1315 (67.9)	0.094
Weight, kg	86.7±20.2	78.4±16.5	<0.001
Heart rate, /min	85.0±10.8	84.7±10.6	0.475
Respiratory rate, /min	17.2±3.1	17.2±3.0	0.999
Glucose, mg/dL	133.4±23.6	128.6±22.2	<0.001
SBP, mmHg	112.7±10.5	114.0±10.8	<0.001
DBP, mmHg	56.5±6.9	57.9±6.9	<0.001
CVP, mmHg	11.2±3.7	9.8±3.1	<0.001
Urine output, mL	1735.5 (1245.0-2384.3)	2550.0 (1930.0-3355.0)	<0.001
pO_2, mmHg	309.0 (204.0-379.0)	323.0 (224.0-389.0)	0.009
Sedative	2116 (86.3)	1591 (82.2)	<0.001
Ventilation	2183 (89.0)	1653 (85.4)	<0.001
Furosemide	341 (13.9)	334 (17.3)	0.002
Atrial fibrillation	1074 (43.8)	621 (32.1)	<0.001
Congestive heart failure	673 (27.4)	345 (17.8)	<0.001
Stroke	132 (5.4)	126 (6.5)	0.121
Left heart catheterization	762 (31.1)	526 (27.2)	0.005

Data are depicted as the mean ± standard deviation, the median (interquartile range) or a number (percentage). Continuous data were compared with Student's t test or the rank-sum test, while categorical data were compared using the chi-square test. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; pO_2, partial pressure of oxygen; AKI, acute kidney injury.

Table 3 Variables in the LASSO regression and multivariate logistic regression models

Variables	LASSO	Logistic		
	β	β	OR (95% CI)	*P*
Age	0.011221	0.017	1.017 (1.010-1.023)	<0.001
Male	-0.165641	-0.404	0.667 (0.568-0.784)	<0.001
Weight	0.023091	0.031	1.032 (1.027-1.037)	<0.001
Heart rate	0.000058	0.007	1.007 (1.000-1.014)	0.055
Respiratory rate	-0.006347	-0.042	0.959 (0.936-0.982)	0.001
Glucose	0.000846	0.002	1.002 (0.999-1.005)	0.181
SBP	-0.004721	-0.010	0.990 (0.983-0.997)	0.007
DBP	-0.009688	-0.015	0.985 (0.974-0.997)	0.011
CVP	0.063826	0.072	1.075 (1.051-1.099)	<0.001
Urine output	-0.000603	-0.001	0.999 (0.999-0.999)	<0.001
pO_2	-0.000127	-0.001	0.999 (0.998-1.000)	0.001
Sedative	0.173715	0.340	1.405 (1.032-1.912)	0.031
Ventilation	0.093818	0.189	1.209 (0.862-1.694)	0.272
Furosemide	-0.484207	-0.757	0.469 (0.387-0.569)	<0.001
Atrial fibrillation	0.193466	0.279	1.322 (1.139-1.536)	<0.001
Congestive heart failure	0.207495	0.305	1.357 (1.143-1.611)	<0.001
Stroke	-0.021989	-0.254	0.776 (0.580-1.038)	0.087
Left heart catheterization	0.043483	0.166	1.181 (1.014-1.376)	0.033

LASSO, least absolute shrinkage and selection operator; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; pO_2, partial pressure of oxygen.

Figure legends

Figure 1 Flow chart of enrolled subjects.

A total of 6271 CSRU stay records were enrolled in this study. ICU, intensive care unit; CSRU, cardiac surgery recovery unit.

Figure 2 LASSO coefficient profiles of variables and misclassification errors for different models.

The upper panel presents the associations between the coefficients of variables and the log lambda value. Each line corresponds to one distinct variable. With increasing log lambda, the coefficient of the variable tended toward 0. The lower panel presents the selection of the applicable model. Vertical lines were drawn at the optimal values by adopting the minimum criteria (dashed line) and the SE of the minimum criteria (dotted line, the 1 − SE criteria). In our study, the lambda value was chosen according to the 1 − SE criteria. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Figure 3 Clinical score for the prediction of severe AKI in CSRU patients.

All 14 selected variables, including age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO_2, sedative usage, furosemide, atrial fibrillation, congestive heart failure and left heart catheterization, were given corresponding points based on their values. The total points of these variables corresponded to the predicted probability of severe AKI in the CSRU. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit.

Figure 4 Performance evaluation of the severe AKI prediction model.

ROC curves in the primary cohort (A) and validation cohort (B). The AUCs of the model in the primary and validation cohorts were 0.779 and 0.778, respectively. Calibration curves in the primary cohort (C) and validation cohort (D). The observed values were close to the ideal values, indicating a satisfactory forecasting performance of the clinical score model. Decision curve analyses in the primary cohort (E) and validation cohort (F), showing the net benefit from the model. AKI, acute kidney failure; ROC, receiver operator characteristic curve; AUC, area under the receiver operating characteristic curve.

Supplementary Figure 1 Nomogram for prediction of severe AKI in CSRU patients.

All 14 selected variables, namely, age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO_2, sedative usage, furosemide, atrial fibrillation, congestive heart failure and left heart catheterization, were given corresponding points based on their values. The total points of these variables corresponded to the predicted probability of severe AKI in the CSRU patients. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit.

Supplementary Figure 2 Performance evaluation of the model without urine output.

ROC curves in the primary cohort (A) and validation cohort (B). After excluding urine output from the model, the AUCs of the model in the primary and validation cohorts were 0.713 and 0.718, respectively. ROC, receiver operator characteristic curve; AUC, area under the receiver

operating characteristic curve.

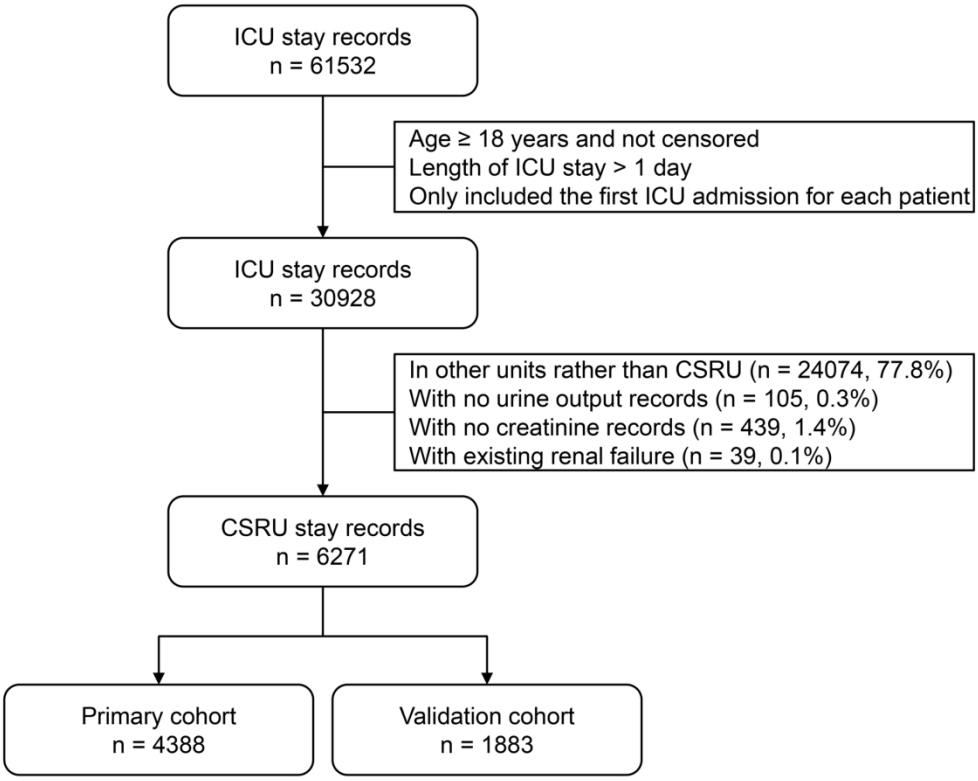

Figure 1 Flow chart of enrolled subjects.
A total of 6271 CSRU stay records were enrolled in this study. ICU, intensive care unit; CSRU, cardiac surgery recovery unit.

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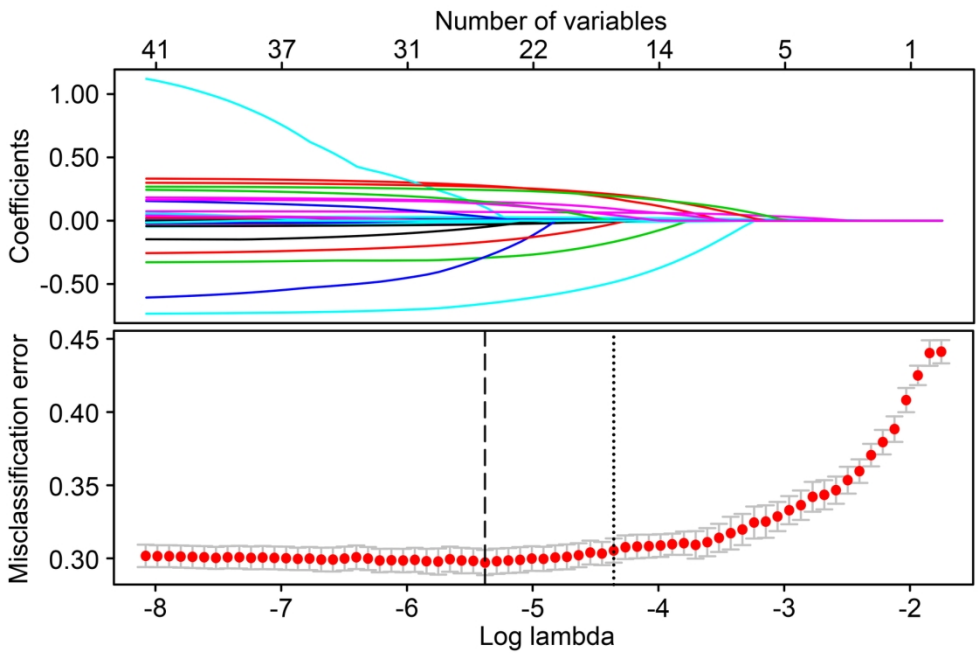

Figure 2 LASSO coefficient profiles of variables and misclassification errors for different models. The upper panel presents the associations between the coefficients of variables and the log lambda value. Each line corresponds to one distinct variable. With increasing log lambda, the coefficient of the variable tended toward 0. The lower panel presents the selection of the applicable model. Vertical lines were drawn at the optimal values by adopting the minimum criteria (dashed line) and the SE of the minimum criteria (dotted line, the 1 − SE criteria). In our study, the lambda value was chosen according to the 1 − SE criteria. LASSO, least absolute shrinkage and selection operator; SE, standard error.

162x107mm (300 x 300 DPI)

Age, years	10	20	30	40	50	60	70	80	90				
Score	0	2	4	6	8	10	12	14	16				
Sex	Male	Female											
Score	0	5											
Weight, kg	20	40	60	80	100	120	140	160	180	200	220	240	260
Score	0	8	15	23	31	38	46	54	62	69	77	85	92
Respiratory rate, /min	5	10	15	20	25	30	35						
Score	14	11	9	7	5	2	0						
SBP, mmHg	70	80	90	100	110	120	130	140	150	160	170	180	
Score	15	14	13	11	10	8	7	6	4	3	1	0	
DBP, mmHg	20	30	40	50	60	70	80	90	100	110			
Score	15	13	11	10	8	6	5	3	2	0			
CVP, mmHg	0	5	10	15	20	25	30	35					
Score	5	9	14	18	23	27	32	36					
Urine output, mL	0	1000	2000	3000	4000	5000	6000	7000	8000	9000	10000		
Score	84	76	67	59	51	42	34	25	17	8	0		
pO2, mmHg	0	100	200	300	400	500	600	700	800				
Score	10	9	8	7	5	4	3	1	0				
Sedative	No	Yes											
Score	0	6											
Furosemide	No	Yes											
Score	10	0											
Atrial fibrillation	No	Yes		**Total scores**			125	135	151	161	171	188	197
Score	0	3		**Probability of severe AKI**			0.05	0.10	0.30	0.50	0.70	0.90	0.95
Congestive heart failure	No	Yes											
Score	0	4											
Left heart catheterization	No	Yes											
Score	0	2											

Figure 3 Clinical score for the prediction of severe AKI in CSRU patients.
All 14 selected variables, including age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO2, sedative usage, furosemide, atrial fibrillation, congestive heart failure and left heart catheterization, were given corresponding points based on their values. The total points of these variables corresponded to the predicted probability of severe AKI in the CSRU. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit.

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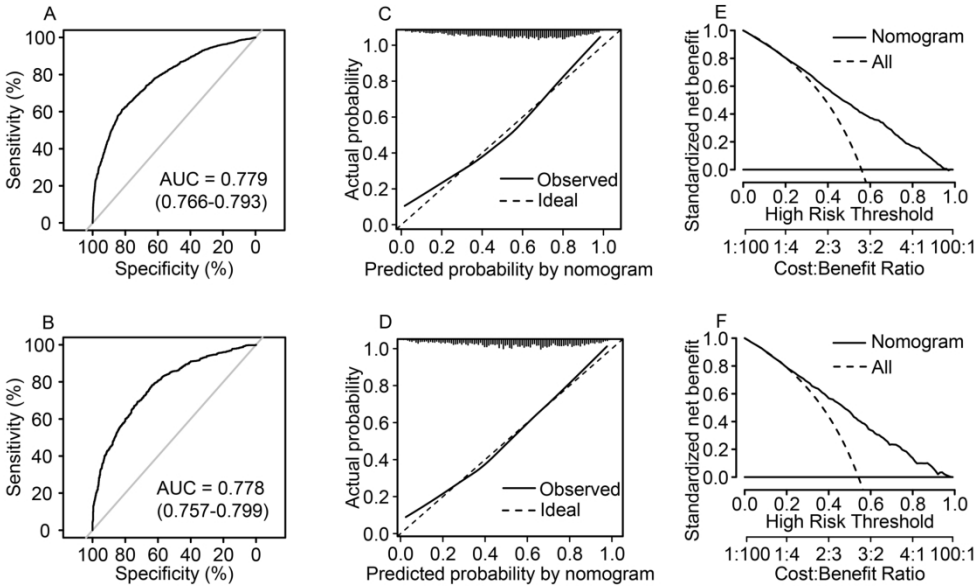

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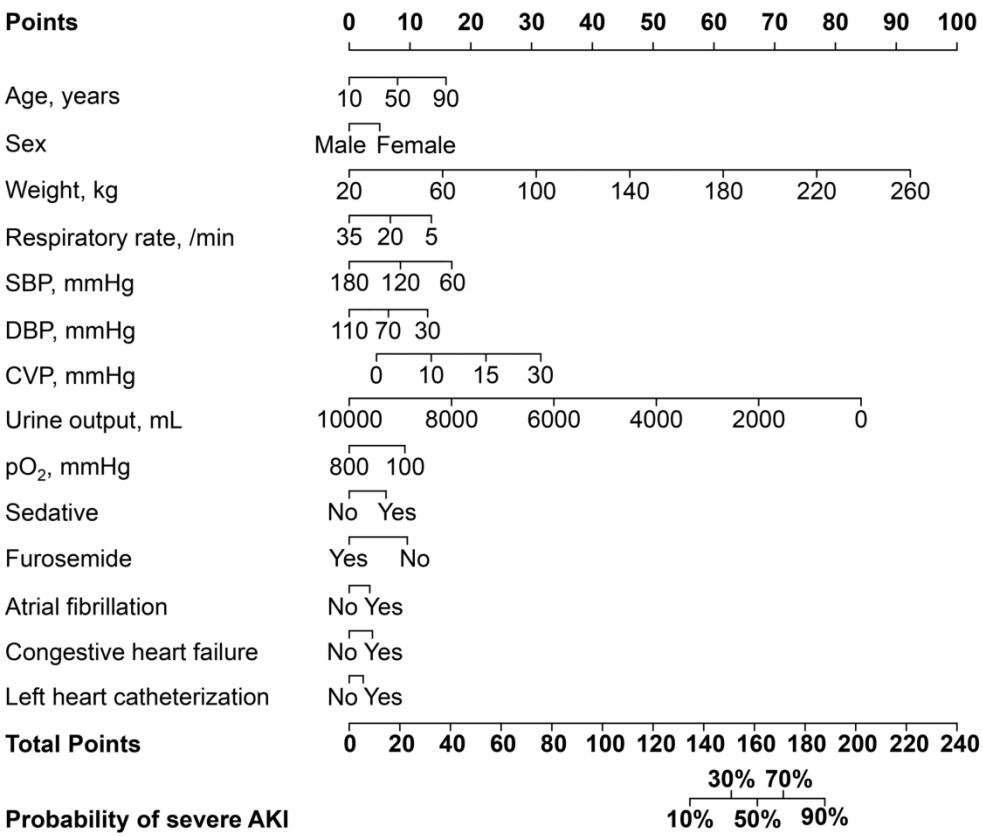

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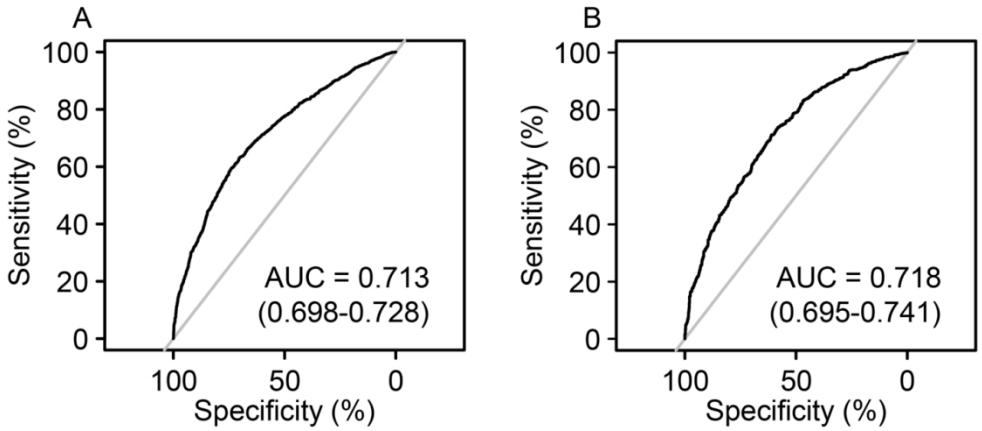

122x55mm (300 x 300 DPI)

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2-3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	D;V	Describe eligibility criteria for participants.	5
	5c	D;V	Give details of treatments received, if relevant.	5
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5-6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	5-6
Sample size	8	D;V	Explain how the study size was arrived at.	5
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	6
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	6
	10c	V	For validation, describe how the predictions were calculated.	6
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	6
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	6
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	6
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	7
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	7
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	7
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	8
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	8
	15b	D	Explain how to the use the prediction model.	8
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	8
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	8
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	11
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	10
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	9-10
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	9
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	12
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	12

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

A LASSO-derived clinical score to predict severe acute kidney injury in the cardiac surgery recovery unit: A large retrospective cohort study using the MIMIC database

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Secondary Subject Heading:	Cardiovascular medicine, Renal medicine
Keywords:	Acute renal failure < NEPHROLOGY, Cardiac surgery < SURGERY, Adult intensive & critical care < ANAESTHETICS

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A LASSO-derived clinical score to predict severe acute kidney injury in the cardiac surgery recovery unit: A large retrospective cohort study using the MIMIC database

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Abstract

Objectives We aimed to develop an effective tool for predicting severe acute kidney injury (AKI) in patients admitted to the cardiac surgery recovery unit (CSRU).

Design A retrospective cohort study.

Setting Data were extracted from the Medical Information Mart for Intensive Care (MIMIC)-III database, consisting of critically ill participants between 2001 and 2012 in the USA.

Participants A total of 6271 patients admitted to the CSRU were enrolled from the MIMIC-III database.

Primary and secondary outcome Stage 2 to 3 AKI.

Result As identified by least absolute shrinkage and selection operator (LASSO) and logistic regression, risk factors for AKI included age, sex, weight, respiratory rate, systolic blood pressure, diastolic blood pressure, central venous pressure, urine output, partial pressure of oxygen, sedative use, furosemide use, atrial fibrillation, congestive heart failure, and left heart catheterization, all of which were used to establish a clinical score. The areas under the receiver operating characteristic curve of the model were 0.779 (95% confidence interval: 0.766-0.793) for the primary cohort and 0.778 (95% confidence interval: 0.757-0.799) for the validation cohort. The calibration curves showed good agreement between the predictions and observations. Decision curve analysis demonstrated that the model could achieve a net benefit.

Conclusion A clinical score built by using LASSO regression and logistic regression to screen multiple clinical risk factors was established to estimate the probability of severe AKI in CSRU patients. This may be an intuitive and practical tool for severe AKI prediction in the CSRU.

Key words: acute kidney injury, LASSO, clinical score, cardiac surgery recovery unit, prediction

Strengths and limitations of this study

Least absolute shrinkage and selection operator regression and multivariable logistic regression were used to establish a clinical score model.

The performance of this novel clinical score model in both the primary cohort and validation cohort was evaluated using the area under the receiver operating characteristic curve, calibration curves, and decision curve analysis.

This novel clinical score model might not be suitable for those with a renal failure history.

External validation of this novel clinical score model was lacking.

Introduction

Acute kidney injury (AKI), a common complication in patients admitted to the intensive care unit worldwide[1 2], is associated with adverse short- and long-term prognoses[3]. It has been reported that more than half of patients in the cardiac surgery recovery unit (CSRU) suffer from AKI of some stage[4], which is associated with high mortality and rehospitalization rates[5]. The early and rapid diagnosis and treatment of AKI may help reduce mortality and rehospitalization rates. Although several biomarkers have been used for the early diagnostic and prognostic prediction of AKI[6 7], the clinical utilization of these biomarkers has been limited. When the levels of these biomarkers increase, renal injury occurs. Thus, identifying critically ill patients at high risk of AKI is an important part of the overall management of CSRU patients.

Graphical calculation devices, which are presented as a scale or score that incorporate possible risk factors to make clinical prognostic predictions, have become increasingly popular.

It has been extensively used to predict the probability of death or recurrence events for a patient with cancer[8]. Recently, some researchers established a clinical prediction model for forecasting the occurrence of AKI in patients undergoing cardiac surgery[9]. However, that small, single-center study did not exclude patients with chronic kidney disease and thus probably overestimated the occurrence of AKI; additionally, only logistic regression for variable selection was used. By machine learning, a model was established to predict cardiac surgery–associated AKI, although the sample was small and urine output was neglected[10]. Another study used a convolutional neural network model to predict severe AKI in the intensive care unit (ICU), while patients with a previous diagnosis of chronic kidney disease were not excluded[11].

Least absolute shrinkage and selection operator (LASSO) regression is of great strength for variable selection because it can efficiently address the potential association between covariates, such as collinearity[12]. Accordingly, in this study, we performed LASSO regression to select variables and built a logistic regression model to identify independent risk factors for severe AKI in patients admitted to the CSRU. We aimed to determine the risk factors for severe AKI and develop a clinical score for evaluating the probability that patients undergoing critical cardiac care will acquire severe AKI.

Methods

Data source and ethics approval

The data were extracted from the Medical Information Mart for Intensive Care (MIMIC)-III dataset. As a large and publicly available database, MIMIC-III comprises the clinical information for 61532 ICU stay cases between 2001 and 2012. The use of the MIMIC-III

database was approved by the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center[13]. Because the information used in the study was from a publicly deidentified database, the informed consent requirement was waived.

Study population

Adult ICU stays longer than 1 day were included. When a patient had multiple ICU admissions, only the first medical record was selected for the study. The exclusion criteria were as follows: patients in units other than the CSRU (n = 24074, 77.8%); patients with no urine output records (n = 105, 0.3%); patients with no creatinine data (n = 439, 1.4%); and patients with existing renal failure (n = 39, 0.1%) (Figure 1). During the CSRU stay, all creatinine and urine output records were extracted, and AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[14]. Baseline serum creatinine was defined as the lowest creatinine in the past 7 days. Both urine output and serum creatinine criteria were used to identify AKI. Information about renal replacement therapy was not considered in this study. Severe AKI was defined as stage 2 or stage 3 AKI under the KDIGO criteria. Patients in the CSRU were screened, and a total of 6271 patients were included. Chronologically, the first 70% of patients were allocated to the primary cohort, and the last 30% were allocated to the validation cohort. Subsequently, we established a clinical score model by using the primary cohort data and validated the model by using the validation cohort.

Variable extraction

The following variables were extracted.

Demographics: age (years), sex, height (cm), and weight (kg).

Vital signs: heart rate (/min), respiratory rate (/min), temperature (℃), saturation of peripheral oxygen (%), blood glucose level (mg/dL), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), central venous pressure (CVP, mmHg), and mean artery pressure (mmHg). The mean value of vital signs in the 24 hours after admission was included for analysis.

Laboratory tests: white blood cell count (×10^9/L), hemoglobin (g/dL), platelets (×10^9/L), chloride (mmol/L), sodium (mmol/L), blood urea nitrogen (BUN, mg/dL), bicarbonate (mmol/L), pH, partial pressure of oxygen (pO_2, mmHg), partial pressure of carbon dioxide (pCO_2, mmHg), creatinine (mg/dL), and potassium (mmol/L). The values of laboratory tests in the first 24 hours after admission were used for the analysis. In addition, 24-hour urine output was extracted.

Procedures: administration of furosemide, use of sedative, ventilation, vasopressor, cardiopulmonary bypass, coronary artery bypass grafting, left heart catheterization. The sedative drugs in this study included midazolam, fentanyl, propofol, and midazolam.

Comorbidities: coronary artery disease, congestive heart failure, atrial fibrillation, stroke, diabetes, renal disease, liver disease, chronic obstructive pulmonary disease, and malignancy.

All variables were collected in the initial 24 hours after admission to predict severe AKI as early as possible. The frequency of missing values for each variable was less than 15%. The missing values were filled in by the random forest method using R software.

Statistical analysis

Continuous variables are denoted as the mean ± SD or the median (interquartile range), whereas categorical variables are expressed as numbers (percentages). Continuous data were compared with Student's t test or the rank-sum test, while categorical data were compared using the chi-square test.

In this study, LASSO was performed for variable selection. LASSO regression is a compression estimation used to address the collinearity between covariates. When there are several collinear predictors, LASSO selects only one and ignores the others or zeroes out some regression coefficients. Cross-validation was used during LASSO regression, and 1 − standard error criterion was used to select lambda. Namely, the value of lambda was identified when the cross-validated error was within one standard error of the minimum. Odds ratios (ORs) with 95% confidence intervals (95% CIs), statistics describing the strength of the association between disease and exposure, were calculated by logistic regression, thus estimating the association of independent risk factors with AKI. Finally, a clinical score model was established based on the above analysis, which was further validated with C-indices, accuracy, sensitivity, specificity, positive predictive value, negative predictive value, receiver operating characteristic (ROC) curves, the areas under the ROC curves (AUCs), calibration curves, and decision curve analysis. We used 10-fold cross validation to identify the optimal clinical score model. Briefly, the primary cohort was randomly divided into 10 roughly equal-sized groups. One group was taken as a test dataset, and the remaining groups were used as a training dataset. The model was fitted on the training dataset and evaluated on the test dataset. After repeating the process 10 times, the optimal model with the best performance was identified.

SPSS software (version 23.0, IBM, NY, USA) and R software (version 3.6.3, R

Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. The packages used in this study included *missForest*, *glmnet*, *rms*, *pROC*, *caret*, and *rmda*. A two-sided $P<0.05$ was considered statistically significant.

Patient and public involvement

Patients and/or the public were not directly involved in this study.

Results

Patients with severe AKI comprised 55.9% (2452/4388) and 54.2% (1020/1883) of the primary and validation cohorts, respectively. No significant difference in the severe AKI rate was observed between the two cohorts ($P=0.213$). Except for SBP (primary cohort, 113.3 mmHg vs. validation cohort, 132.4 mmHg, $P=0.040$), no clinical characteristics showed a significant difference between the primary and validation cohorts (Table 1).

In the primary cohort, patients with severe AKI were older, had higher weights and had higher blood glucose level than those without severe AKI ($P < 0.001$). SBP and DBP were significantly lower (112.7 mmHg vs. 114.0 mmHg and 56.6 mmHg vs. 57.9 mmHg, respectively), while CVP was significantly higher (11.2 mmHg vs. 9.8 mmHg) in the severe AKI group ($P<0.001$). Urine output and pO_2 were lower in the severe AKI group ($P < 0.01$). Drug administration was also different, namely, severe AKI patients received sedatives, ventilation, and furosemide significantly more often ($P<0.001$). The stroke prevalence rates were the same, but a higher prevalence of atrial fibrillation, congestive heart failure and left heart catheterization was observed in severe AKI patients ($P<0.05$) (Table 2).

To confirm the possible risk factors for severe AKI, we performed LASSO regression to select variables. A total of 18 variables were enrolled for further analysis according to the 1 − standard error criterion (Figure 2). Then, we conducted logistic regression analysis based on the LASSO results. A total of 14 variables were shown to be associated with severe AKI (Table 3).

Next, we included the above significant factors to build a clinical score based on the logistic regression model (Figure 3). Each level of every variable was assigned a score. By adding the scores for all of the selected variables, the total score was obtained. By checking the number corresponding to the total scores, the probability of severe AKI can be estimated for a given patient. Another nomogram version with scales instead of numbers is supplied as well (Supplementary Figure 1).

The C-indices were 0.779 for the primary cohort and 0.778 for the validation cohort. The ROC curves demonstrated that the model had good discriminative ability in both the primary cohort (AUC: 0.779, 95% CI: 0.766-0.793) and the validation cohort (AUC: 0.778, 95% CI: 0.757-0.799) (Table 4). Calibration plots showed that the apparent curves were adjacent to the ideal curves in both the primary and validation groups. Finally, decision curve analysis was performed to compare the clinical usability and benefits of the model. The decision curves showed acceptable net benefits across a range of high risks of severe AKI in the primary and validation cohorts (Figure 4).

We also evaluated the model performance after excluding the variable of urine output. Without urine output information, the model also showed acceptable discriminative ability in both the primary cohort (AUC: 0.713, 95% CI: 0.698-0.728) and the validation cohort (AUC:

0.718, 95% CI: 0.695-0.741) (Supplementary Table 1). For patients without suffering AKI in the initial 24 hours after admission, the model performed with an AUC of 0.680 (95% CI: 0.651-0.709) in the primary cohort and an AUC of 0.673 (95% CI: 0.630-0.715) (Supplementary Table 2).

Discussion

AKI is a complicated clinical syndrome characterized by reduced urine production and/or rapid increases in serum creatinine[15]. AKI has been reported to be positively associated with short-term mortality in CSRU populations[5 16]. Delayed diagnosis of AKI is an independent risk factor for nosocomial death[17]. Therefore, the early identification of patients at risk for AKI might help to reduce short-term mortality, improve prognosis, and reduce the health care burden.

In this study, we extracted the clinical information of 6271 patients from the MIMIC-III database. We identified the following 14 possible risk factors for severe AKI by LASSO regression and logistical regression: age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO_2, sedative use, furosemide, atrial fibrillation, congestive heart failure, and left heart catheterization. Subsequently, a clinical score model was constructed by quantifying the weight of the aforementioned variables. The clinical score model was well fitted, as evaluated by the AUC, calibration curves and decision curve analysis in both the primary and validation cohorts. The model could calculate a severe AKI probability immediately after the initial 24 hours and might help clinicians perform early intervention.

Several scoring systems and prognostic models have been built to predict AKI. Scoring systems such as the Cleveland Clinic Score[18] and the Mehta Score[19] only consider AKI patients

requiring dialysis and thus might miss patients with subclinical AKI. Additionally, clinical prediction models have been used to forecast AKI in patients undergoing cardiac surgery[9] or coronary angiography[20]. These studies enrolled both mild and severe AKI patients. Our model was generated from the MIMIC-III database, with a larger sample size and more variables. This study predicted only severe AKI, which might be more attractive for clinical practice. Moreover, the primary cohort and validation cohort were assigned by admission time. According to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement, nonrandom assignment by time is a stronger design feature for evaluating model performance than random assignment[21].

LASSO regression is a popular variable selection algorithm for multicollinear data or high-dimensional data[22]. LASSO has been widely used for clinical prediction. For example, via LASSO, researchers have built a clinical model to predict the diagnosis and prognosis of colon cancer[23]. A radiomics signature using LASSO has been developed to evaluate survival in patients with non-small-cell lung cancer[24]. LASSO has been used to predict AKI in patients with hematologic tumors, patients suffering from cardiac surgery or patients hospitalized in the neurosurgical intensive care unit[12 22 25]. In the present study, based on clinical profiles, LASSO was performed to select relevant coefficients from a multitude of variables, simultaneously removing all unrelated variables. Through dimensionality reduction using LASSO, 42 clinical variables were screened down to 14 risk factors, according to the 1 − standard error criterion.

Among those 14 variables, older age and obesity were independent risk factors for AKI, as indicated by previous investigations[26 27]. Additionally, hypotension has been reported to be associated with new-onset AKI in ICU patients with shock[28]. High CVP, indicating fluid

overload, is another factor affecting AKI[29]. Consistent with previous studies, these risk factors were included in the clinical score model and given a weighted score. Reduced urine output is a clinical manifestation of AKI and is also an important factor underlying the poor prognosis of AKI. In this study, decreased urine output was one of the most important predictors of AKI in CSRU patients. Overall, the clinical score model contained 14 variables, more than half of which have been reported to be associated with AKI. In addition, ROC curves, calibration curves, and decision curve analysis showed consistent results in both the primary and validation cohorts, showing that the clinical score model could be an effective and reliable tool for predicting the risk of severe AKI.

Several limitations of our study must be noted. First, this study was based on the MIMIC-III database, whose data were collected between 2001 and 2012. Some therapies might not meet the latest guidelines and some newer medicines might not be included. Because of the single-center nature of the data, the performance of our model might vary when applied to other regions. The potential residual confounding by variables not recorded in this database could not be evaluated. Second, only patients without existing renal failure were included in this study. Thus, this novel score model might not be suitable for those with a renal failure history. Third, missing values were filled by the random forest method, which might lead to biased regression coefficient estimates[30]. Therefore, further studies are needed to verify our model. Fourth, our model was designed to be used immediately after the initial 24 hours of admission, and it may not work for patients who suffer AKI within those initial 24 hours.

Conclusion

In conclusion, this study established and validated a novel clinical score by using LASSO regression and logistic regression to screen for multiple clinical risk factors to estimate the probability of severe AKI in CSRU patients. This clinical score model can be an intuitive and reliable predictive tool that might help in individualized clinical decision-making and risk management for severe AKI.

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Table 1 Baseline characteristics of the enrolled subjects in the primary and validation cohorts.

	Primary cohort	Validation cohort	*P*
n	4388	1883	
Age, years	66.0±12.8	65.9±13.3	0.715
Male	2921 (66.6)	1229 (65.3)	0.332
Weight, kg	83.0±19.1	83.2±20.0	0.785
Heart rate, /min	84.9±10.7	84.6±10.8	0.357
Respiratory rate, /min	17.2±3.1	17.2±3.0	0.914
Glucose, mg/dL	131.2±23.2	132.4±23.2	0.060
SBP, mmHg	113.3±10.7	113.9±10.8	0.040
DBP, mmHg	57.1±6.9	57.3±7.0	0.244
CVP, mmHg	10.6±3.5	10.7±3.6	0.191
Urine output, mL	2075.0 (1480.0-2880.0)	2080.0 (1457.0-2900.0)	0.949
pO_2, mmHg	314.0 (211.0-383.0)	308.0 (206.0-386.0)	0.168
Sedative	3707 (84.5)	1593 (84.6)	0.905
Ventilation	3836 (87.4)	1642 (87.2)	0.811
Furosemide	675 (15.4)	292 (15.5)	0.901
Atrial fibrillation	1695 (38.6)	754 (40.0)	0.293
Congestive heart failure	1018 (23.2)	442 (23.5)	0.814
Stroke	258 (5.9)	108 (5.7)	0.823
Left heart catheterization	1288 (29.4)	551 (29.3)	0.942
Severe AKI	2452 (55.9)	1020 (54.2)	0.213

The data are depicted as the mean ± standard deviation, the median (interquartile range) or a number (percentage). Continuous data were compared with Student's t test or the rank-sum test, while categorical data were compared using the chi-square test. SBP, systolic blood pressure;

DBP, diastolic blood pressure; CVP, central venous pressure; pO_2, partial pressure of oxygen; AKI, acute kidney injury.

Table 2 Baseline characteristics of the severe AKI and non-severe AKI groups in the primary cohort.

	Severe AKI	Non-severe AKI	*P*
n	2452	1936	
Age, years	67.4±12.2	64.3±13.3	<0.001
Male	1606 (65.5)	1315 (67.9)	0.094
Weight, kg	86.7±20.2	78.4±16.5	<0.001
Heart rate, /min	85.0±10.8	84.7±10.6	0.475
Respiratory rate, /min	17.2±3.1	17.2±3.0	0.999
Glucose, mg/dL	133.4±23.6	128.6±22.2	<0.001
SBP, mmHg	112.7±10.5	114.0±10.8	<0.001
DBP, mmHg	56.5±6.9	57.9±6.9	<0.001
CVP, mmHg	11.2±3.7	9.8±3.1	<0.001
Urine output, mL	1735.5 (1245.0-2384.3)	2550.0 (1930.0-3355.0)	<0.001
pO_2, mmHg	309.0 (204.0-379.0)	323.0 (224.0-389.0)	0.009
Sedative	2116 (86.3)	1591 (82.2)	<0.001
Ventilation	2183 (89.0)	1653 (85.4)	<0.001
Furosemide	341 (13.9)	334 (17.3)	0.002
Atrial fibrillation	1074 (43.8)	621 (32.1)	<0.001
Congestive heart failure	673 (27.4)	345 (17.8)	<0.001
Stroke	132 (5.4)	126 (6.5)	0.121
Left heart catheterization	762 (31.1)	526 (27.2)	0.005

The data are depicted as the mean ± standard deviation, the median (interquartile range) or a number (percentage). Continuous data were compared with Student's t test or the rank-sum test, while categorical data were compared using the chi-square test. SBP, systolic blood pressure;

DBP, diastolic blood pressure; CVP, central venous pressure; pO_2, partial pressure of oxygen; AKI, acute kidney injury.

Table 3 Variables in the LASSO regression and multivariate logistic regression models.

Variables	LASSO	Logistic		
	β	*β*	OR (95% CI)	*P*
Age	0.011221	0.017	1.017 (1.010-1.023)	<0.001
Male	-0.165641	-0.404	0.667 (0.568-0.784)	<0.001
Weight	0.023091	0.031	1.032 (1.027-1.037)	<0.001
Heart rate	0.000058	0.007	1.007 (1.000-1.014)	0.055
Respiratory rate	-0.006347	-0.042	0.959 (0.936-0.982)	0.001
Glucose	0.000846	0.002	1.002 (0.999-1.005)	0.181
SBP	-0.004721	-0.010	0.990 (0.983-0.997)	0.007
DBP	-0.009688	-0.015	0.985 (0.974-0.997)	0.011
CVP	0.063826	0.072	1.075 (1.051-1.099)	<0.001
Urine output	-0.000603	-0.001	0.999 (0.999-0.999)	<0.001
pO_2	-0.000127	-0.001	0.999 (0.998-1.000)	0.001
Sedative	0.173715	0.340	1.405 (1.032-1.912)	0.031
Ventilation	0.093818	0.189	1.209 (0.862-1.694)	0.272
Furosemide	-0.484207	-0.757	0.469 (0.387-0.569)	<0.001
Atrial fibrillation	0.193466	0.279	1.322 (1.139-1.536)	<0.001
Congestive heart failure	0.207495	0.305	1.357 (1.143-1.611)	<0.001
Stroke	-0.021989	-0.254	0.776 (0.580-1.038)	0.087
Left heart catheterization	0.043483	0.166	1.181 (1.014-1.376)	0.033

LASSO, least absolute shrinkage and selection operator; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; pO_2, partial pressure of oxygen.

Table 4 Model performance in the primary and validation cohorts.

	AUC (95% CI)	Accuracy (95% CI)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Cutoff value
Primary cohort	0.779 (0.766-0.793)	0.702 (0.688-0.715)	0.609	0.820	0.811	0.623	0.566
Validation cohort	0.778 (0.757-0.799)	0.715 (0.694-0.735)	0.781	0.637	0.718	0.722	0.065

AUC, area under the receiver operating characteristic curve; CI, confidence interval.

Figure legends

Figure 1 Flow chart of enrolled subjects.

A total of 6271 CSRU stay records were enrolled in this study. ICU, intensive care unit; CSRU, cardiac surgery recovery unit.

Figure 2 LASSO coefficient profiles of variables and misclassification errors for different models.

The upper panel presents the associations between the coefficients of variables and the log lambda value. Each line corresponds to one distinct variable. With increasing log lambda, the coefficient of the variable tended toward 0. The lower panel presents the selection of the applicable model. Vertical lines were drawn at the optimal values by adopting the minimum criteria (dashed line) and the SE of the minimum criteria (dotted line, the 1 − SE criteria). In our study, the lambda value was chosen according to the 1 − SE criteria. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Figure 3 Clinical score for the prediction of severe AKI in CSRU patients.

All 14 selected variables, including age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO_2, sedative usage, furosemide, atrial fibrillation, congestive heart failure and left heart catheterization, were given corresponding points based on their values. The total points of these variables corresponded to the predicted probability of severe AKI in the CSRU. SBP, systolic

blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit.

Figure 4 Performance evaluation of the severe AKI prediction model.

ROC curves in the primary cohort (A) and validation cohort (B). The AUCs of the model in the primary and validation cohorts were 0.779 and 0.778, respectively. Calibration curves in the primary cohort (C) and validation cohort (D). The observed values were close to the ideal values, indicating a satisfactory forecasting performance of the clinical score model. Decision curve analyses in the primary cohort (E) and validation cohort (F), showing the net benefit from the model. AKI, acute kidney failure; ROC, receiver operator characteristic curve; AUC, area under the receiver operating characteristic curve.

Supplementary Figure 1 Nomogram for the prediction of severe AKI in CSRU patients.

All 14 selected variables, namely, age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO_2, sedative usage, furosemide, atrial fibrillation, congestive heart failure and left heart catheterization, were given corresponding points based on their values. The total points of these variables corresponded to the predicted probability of severe AKI in the CSRU patients. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit.

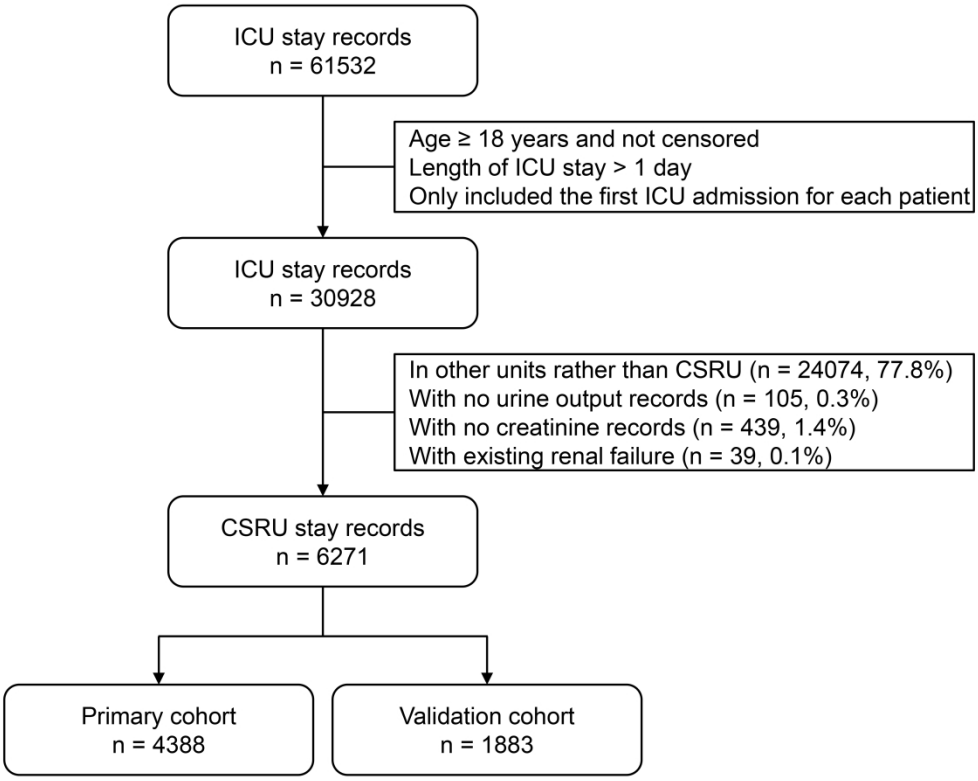


Figure 1 Flow chart of enrolled subjects.
A total of 6271 CSRU stay records were enrolled in this study. ICU, intensive care unit; CSRU, cardiac surgery recovery unit.

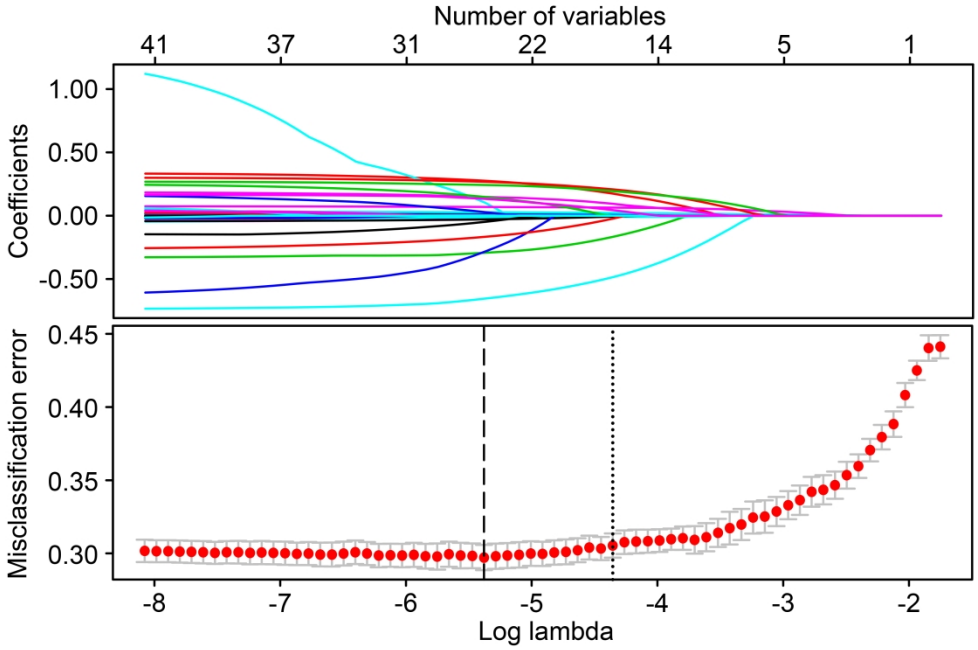
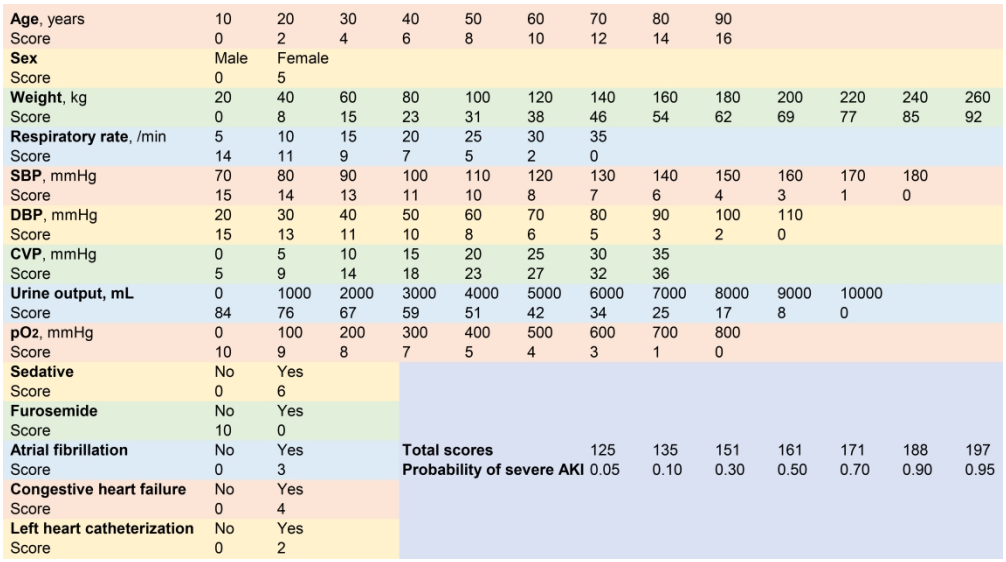


Figure 2 LASSO coefficient profiles of variables and misclassification errors for different models. The upper panel presents the associations between the coefficients of variables and the log lambda value. Each line corresponds to one distinct variable. With increasing log lambda, the coefficient of the variable tended toward 0. The lower panel presents the selection of the applicable model. Vertical lines were drawn at the optimal values by adopting the minimum criteria (dashed line) and the SE of the minimum criteria (dotted line, the 1 − SE criteria). In our study, the lambda value was chosen according to the 1 − SE criteria. LASSO, least absolute shrinkage and selection operator; SE, standard error.



Age, years	10	20	30	40	50	60	70	80	90				
Score	0	2	4	6	8	10	12	14	16				
Sex	Male	Female											
Score	0	5											
Weight, kg	20	40	60	80	100	120	140	160	180	200	220	240	260
Score	0	8	15	23	31	38	46	54	62	69	77	85	92
Respiratory rate, /min	5	10	15	20	25	30	35						
Score	14	11	9	7	5	2	0						
SBP, mmHg	70	80	90	100	110	120	130	140	150	160	170	180	
Score	15	14	13	11	10	8	7	6	4	3	1	0	
DBP, mmHg	20	30	40	50	60	70	80	90	100	110			
Score	15	13	11	10	8	6	5	3	2	0			
CVP, mmHg	0	5	10	15	20	25	30	35					
Score	5	9	14	18	23	27	32	36					
Urine output, mL	0	1000	2000	3000	4000	5000	6000	7000	8000	9000	10000		
Score	84	76	67	59	51	42	34	25	17	8	0		
pO2, mmHg	0	100	200	300	400	500	600	700	800				
Score	10	9	8	7	5	4	3	1	0				
Sedative	No	Yes											
Score	0	6											
Furosemide	No	Yes											
Score	10	0											
Atrial fibrillation	No	Yes		**Total scores**			125	135	151	161	171	188	197
Score	0	3		**Probability of severe AKI**			0.05	0.10	0.30	0.50	0.70	0.90	0.95
Congestive heart failure	No	Yes											
Score	0	4											
Left heart catheterization	No	Yes											
Score	0	2											

Figure 3 Clinical score for the prediction of severe AKI in CSRU patients.
All 14 selected variables, including age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO2, sedative usage, furosemide, atrial fibrillation, congestive heart failure and left heart catheterization, were given corresponding points based on their values. The total points of these variables corresponded to the predicted probability of severe AKI in the CSRU. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit.

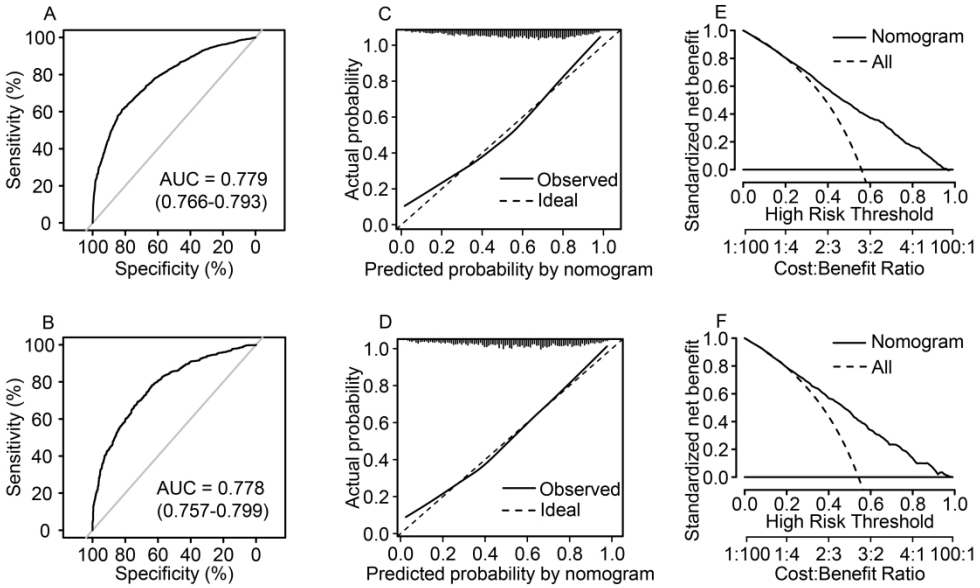
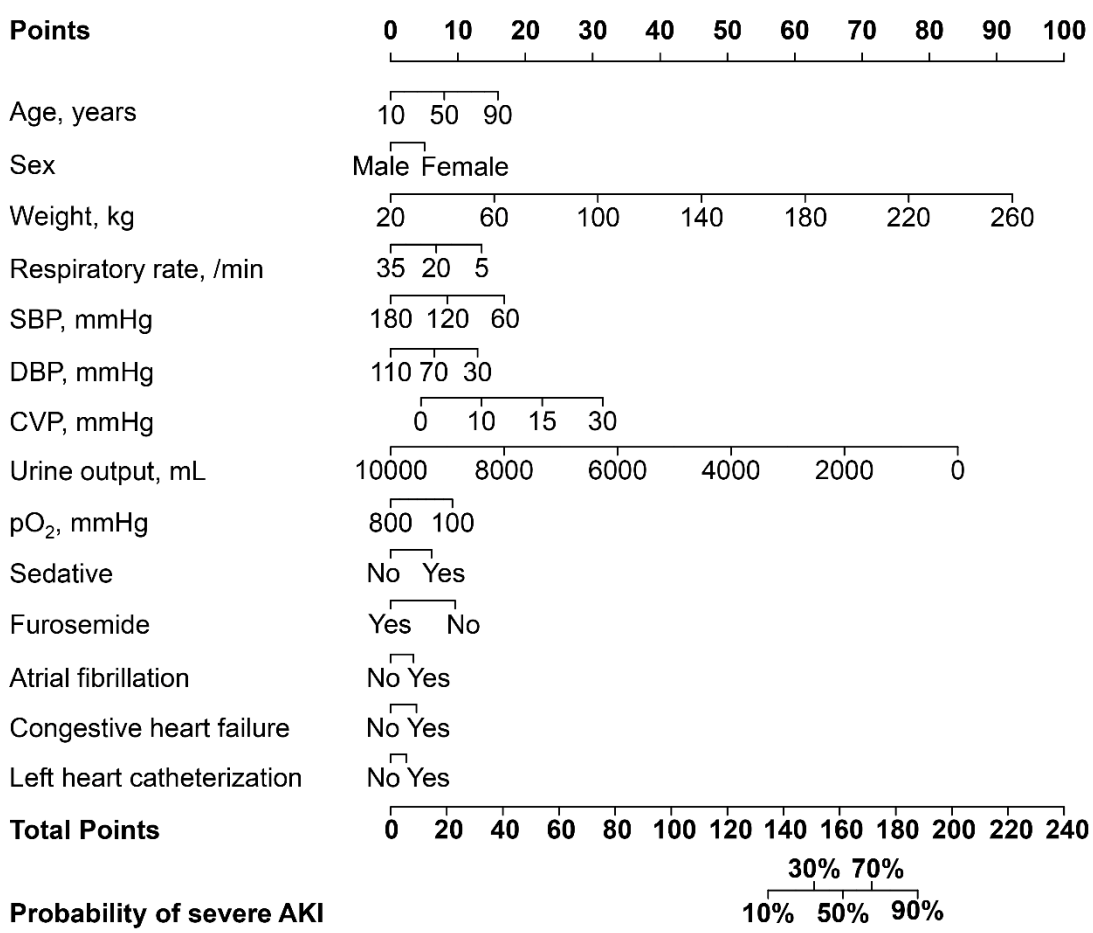


Figure 4 Performance evaluation of the severe AKI prediction model.
ROC curves in the primary cohort (A) and validation cohort (B). The AUCs of the model in the primary and validation cohorts were 0.779 and 0.778, respectively. Calibration curves in the primary cohort (C) and validation cohort (D). The observed values were close to the ideal values, indicating a satisfactory forecasting performance of the clinical score model. Decision curve analyses in the primary cohort (E) and validation cohort (F), showing the net benefit from the model. AKI, acute kidney failure; ROC, receiver operator characteristic curve; AUC, area under the receiver operating characteristic curve.

Supplementary figure and tables



Supplementary Figure 1 Nomogram for the prediction of severe AKI in CSRU patients. All 14 selected variables, namely, age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO_2, sedative usage, furosemide, atrial fibrillation, congestive heart failure and left heart catheterization, were given corresponding points based on their values. The total points of these variables corresponded to the predicted probability of severe AKI in the CSRU patients. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit.

Supplementary Table 1 Performance evaluation of the model without urine output.

	AUC (95% CI)	Accuracy (95% CI)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Cutoff value
Primary cohort (n=4388)	0.713 (0.698-0.728)	0.658 (0.644-0.672)	0.594	0.739	0.743	0.590	0.363
Validation cohort (n=1883)	0.718 (0.695-0.741)	0.666 (0.644-0.687)	0.712	0.610	0.683	0.642	0.095

AUC, area under the receiver operating characteristic curve; CI, confidence interval.

Supplementary Table 2 Model performance in patients without suffering AKI in the initial 24 hours.

	AUC (95% CI)	Accuracy (95% CI)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Cutoff value
Primary cohort (n=1800)	0.680 (0.651-0.709)	0.704 (0.682-0.725)	0.538	0.757	0.412	0.838	-0.943
Validation cohort (n=820)	0.673 (0.630-0.715)	0.637 (0.603-0.670)	0.624	0.641	0.343	0.850	-1.124

AUC, area under the receiver operating characteristic curve; CI, confidence interval.

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2-3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	D;V	Describe eligibility criteria for participants.	5
	5c	D;V	Give details of treatments received, if relevant.	5
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5-6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	5-6
Sample size	8	D;V	Explain how the study size was arrived at.	5
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	6
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	6
	10c	V	For validation, describe how the predictions were calculated.	6
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	6
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	6
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	6
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	7
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	7
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	7
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	8
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	8
	15b	D	Explain how to the use the prediction model.	8
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	8
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	8
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	11
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	10
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	9-10
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	9
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	12
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	12

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

A LASSO-derived clinical score to predict severe acute kidney injury in the cardiac surgery recovery unit: A large retrospective cohort study using the MIMIC database

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A LASSO-derived clinical score to predict severe acute kidney injury in the cardiac surgery recovery unit: A large retrospective cohort study using the MIMIC database

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Abstract

Objectives We aimed to develop an effective tool for predicting severe acute kidney injury (AKI) in patients admitted to the cardiac surgery recovery unit (CSRU).

Design A retrospective cohort study.

Setting Data were extracted from the Medical Information Mart for Intensive Care (MIMIC)-III database, consisting of critically ill participants between 2001 and 2012 in the USA.

Participants A total of 6271 patients admitted to the CSRU were enrolled from the MIMIC-III database.

Primary and secondary outcome Stage 2 to 3 AKI.

Result As identified by least absolute shrinkage and selection operator (LASSO) and logistic regression, risk factors for AKI included age, sex, weight, respiratory rate, systolic blood pressure, diastolic blood pressure, central venous pressure, urine output, partial pressure of oxygen, sedative use, furosemide use, atrial fibrillation, congestive heart failure, and left heart catheterization, all of which were used to establish a clinical score. The areas under the receiver operating characteristic curve of the model were 0.779 (95% confidence interval: 0.766-0.793) for the primary cohort and 0.778 (95% confidence interval: 0.757-0.799) for the validation cohort. The calibration curves showed good agreement between the predictions and observations. Decision curve analysis demonstrated that the model could achieve a net benefit.

Conclusion A clinical score built by using LASSO regression and logistic regression to screen multiple clinical risk factors was established to estimate the probability of severe AKI in CSRU patients. This may be an intuitive and practical tool for severe AKI prediction in the CSRU.

Key words: acute kidney injury, LASSO, clinical score, cardiac surgery recovery unit, prediction

Strengths and limitations of this study

Least absolute shrinkage and selection operator regression and multivariable logistic regression were used to establish a clinical score model.

The performance of this novel clinical score model in both the primary cohort and validation cohort was evaluated using the area under the receiver operating characteristic curve, calibration curves, and decision curve analysis.

This novel clinical score model might not be suitable for those with a renal failure history.

External validation of this novel clinical score model was lacking.

Introduction

Acute kidney injury (AKI), a common complication in patients admitted to the intensive care unit worldwide[1 2], is associated with adverse short- and long-term prognoses[3]. It has been reported that more than half of patients in the cardiac surgery recovery unit (CSRU) suffer from AKI of some stage[4], which is associated with high mortality and rehospitalization rates[5]. The early and rapid diagnosis and treatment of AKI may help reduce mortality and rehospitalization rates. Although several biomarkers have been used for the early diagnostic and prognostic prediction of AKI[6 7], the clinical utilization of these biomarkers has been limited. When the levels of these biomarkers increase, renal injury occurs. Thus, identifying critically ill patients at high risk of AKI is an important part of the overall management of CSRU patients.

Graphical calculation devices, which are presented as a scale or score that incorporate possible risk factors to make clinical prognostic predictions, have become increasingly popular.

It has been extensively used to predict the probability of death or recurrence events for a patient with cancer[8]. Recently, some researchers established a clinical prediction model for forecasting the occurrence of AKI in patients undergoing cardiac surgery[9]. However, that small, single-center study did not exclude patients with chronic kidney disease and thus probably overestimated the occurrence of AKI; additionally, only logistic regression for variable selection was used. By machine learning, a model was established to predict cardiac surgery–associated AKI, although the sample was small and urine output was neglected[10]. Another study used a convolutional neural network model to predict severe AKI in the intensive care unit (ICU), while patients with a previous diagnosis of chronic kidney disease were not excluded[11].

Least absolute shrinkage and selection operator (LASSO) regression is of great strength for variable selection because it can efficiently address the potential association between covariates, such as collinearity[12]. Accordingly, in this study, we performed LASSO regression to select variables and built a logistic regression model to identify independent risk factors for severe AKI in patients admitted to the CSRU. We aimed to determine the risk factors for severe AKI and develop a clinical score for evaluating the probability that patients undergoing critical cardiac care will acquire severe AKI.

Methods

Data source and ethics approval

The data were extracted from the Medical Information Mart for Intensive Care (MIMIC)-III dataset. As a large and publicly available database, MIMIC-III comprises the clinical information for 61532 ICU stay cases between 2001 and 2012. The use of the MIMIC-III

database was approved by the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center[13]. Because the information used in the study was from a publicly deidentified database, the informed consent requirement was waived.

Study population

Adult ICU stays longer than 1 day were included. When a patient had multiple ICU admissions, only the first medical record was selected for the study. The exclusion criteria were as follows: patients in units other than the CSRU (n = 24074, 77.8%); patients with no urine output records (n = 105, 0.3%); patients with no creatinine data (n = 439, 1.4%); and patients with existing renal failure (n = 39, 0.1%) (Figure 1). During the CSRU stay, all creatinine and urine output records were extracted, and AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[14]. Baseline serum creatinine was defined as the lowest creatinine in the past 7 days. Both urine output and serum creatinine criteria were used to identify AKI. Information about renal replacement therapy was not considered in this study. Severe AKI was defined as stage 2 or stage 3 AKI under the KDIGO criteria. Patients in the CSRU were screened, and a total of 6271 patients were included. Chronologically, the first 70% of patients were allocated to the primary cohort, and the last 30% were allocated to the validation cohort. Subsequently, we established a clinical score model by using the primary cohort data and validated the model by using the validation cohort.

Variable extraction

The following variables were extracted.

Demographics: age (years), sex, height (cm), and weight (kg).

Vital signs: heart rate (/min), respiratory rate (/min), temperature (℃), saturation of peripheral oxygen (%), blood glucose level (mg/dL), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), central venous pressure (CVP, mmHg), and mean artery pressure (mmHg). The mean value of vital signs in the 24 hours after admission was included for analysis.

Laboratory tests: white blood cell count (×10^9/L), hemoglobin (g/dL), platelets (×10^9/L), chloride (mmol/L), sodium (mmol/L), blood urea nitrogen (BUN, mg/dL), bicarbonate (mmol/L), pH, partial pressure of oxygen (pO_2, mmHg), partial pressure of carbon dioxide (pCO_2, mmHg), creatinine (mg/dL), and potassium (mmol/L). The values of laboratory tests in the first 24 hours after admission were used for the analysis. In addition, 24-hour urine output was extracted.

Procedures: administration of furosemide, use of sedative, ventilation, vasopressor, cardiopulmonary bypass, coronary artery bypass grafting, left heart catheterization. The sedative drugs in this study included midazolam, fentanyl, propofol, and midazolam.

Comorbidities: coronary artery disease, congestive heart failure, atrial fibrillation, stroke, diabetes, renal disease, liver disease, chronic obstructive pulmonary disease, and malignancy.

All variables were collected in the initial 24 hours after admission to predict severe AKI as early as possible. The frequency of missing values for each variable was less than 15%. The missing values were filled in by the random forest method using R software.

Statistical analysis

Continuous variables are denoted as the mean ± SD or the median (interquartile range), whereas categorical variables are expressed as numbers (percentages). Continuous data were compared with Student's t test or the rank-sum test, while categorical data were compared using the chi-square test.

In this study, LASSO was performed for variable selection. LASSO regression is a compression estimation used to address the collinearity between covariates. When there are several collinear predictors, LASSO selects only one and ignores the others or zeroes out some regression coefficients. Cross-validation was used during LASSO regression, and 1 − standard error criterion was used to select lambda. Namely, the value of lambda was identified when the cross-validated error was within one standard error of the minimum. Odds ratios (ORs) with 95% confidence intervals (95% CIs), statistics describing the strength of the association between disease and exposure, were calculated by logistic regression, thus estimating the association of independent risk factors with AKI. Finally, a clinical score model was established based on the above analysis, which was further validated with C-indices, accuracy, sensitivity, specificity, positive predictive value, negative predictive value, receiver operating characteristic (ROC) curves, the areas under the ROC curves (AUCs), calibration curves, and decision curve analysis. We used 10-fold cross validation to identify the optimal clinical score model. Briefly, the primary cohort was randomly divided into 10 roughly equal-sized groups. One group was taken as a test dataset, and the remaining groups were used as a training dataset. The model was fitted on the training dataset and evaluated on the test dataset. After repeating the process 10 times, the optimal model with the best performance was identified.

SPSS software (version 23.0, IBM, NY, USA) and R software (version 3.6.3, R

Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. The packages used in this study included *missForest*, *glmnet*, *rms*, *pROC*, *caret*, and *rmda*. A two-sided $P<0.05$ was considered statistically significant.

Patient and public involvement

Patients and/or the public were not directly involved in this study.

Results

Patients with severe AKI comprised 55.9% (2452/4388) and 54.2% (1020/1883) of the primary and validation cohorts, respectively. No significant difference in the severe AKI rate was observed between the two cohorts ($P=0.213$). Except for SBP (primary cohort, 113.3 mmHg vs. validation cohort, 132.4 mmHg, $P=0.040$), no clinical characteristics showed a significant difference between the primary and validation cohorts (Table 1).

In the primary cohort, patients with severe AKI were older, had higher weights and had higher blood glucose level than those without severe AKI ($P < 0.001$). SBP and DBP were significantly lower (112.7 mmHg vs. 114.0 mmHg and 56.6 mmHg vs. 57.9 mmHg, respectively), while CVP was significantly higher (11.2 mmHg vs. 9.8 mmHg) in the severe AKI group ($P<0.001$). Urine output and pO_2 were lower in the severe AKI group ($P < 0.01$). Drug administration was also different, namely, severe AKI patients received sedatives, ventilation, and furosemide significantly more often ($P<0.001$). The stroke prevalence rates were the same, but a higher prevalence of atrial fibrillation, congestive heart failure and left heart catheterization was observed in severe AKI patients ($P<0.05$) (Table 2).

To confirm the possible risk factors for severe AKI, we performed LASSO regression to select variables. A total of 18 variables were enrolled for further analysis according to the 1 − standard error criterion (Figure 2). Then, we conducted logistic regression analysis based on the LASSO results. A total of 14 variables were shown to be associated with severe AKI (Table 3).

Next, we included the above significant factors to build a clinical score based on the logistic regression model (Figure 3). Each level of every variable was assigned a score. By adding the scores for all of the selected variables, the total score was obtained. By checking the number corresponding to the total scores, the probability of severe AKI can be estimated for a given patient.

The C-indices were 0.779 for the primary cohort and 0.778 for the validation cohort. The ROC curves demonstrated that the model had good discriminative ability in both the primary cohort (AUC: 0.779, 95% CI: 0.766-0.793) and the validation cohort (AUC: 0.778, 95% CI: 0.757-0.799) (Table 4). Calibration plots showed that the apparent curves were adjacent to the ideal curves in both the primary and validation groups. Finally, decision curve analysis was performed to compare the clinical usability and benefits of the model. The decision curves showed acceptable net benefits across a range of high risks of severe AKI in the primary and validation cohorts (Figure 4).

We also evaluated the model performance after excluding the variable of urine output. Without urine output information, the model also showed acceptable discriminative ability in both the primary cohort (AUC: 0.713, 95% CI: 0.698-0.728) and the validation cohort (AUC: 0.718, 95% CI: 0.695-0.741) (Supplementary Table 1). For patients without suffering AKI in

the initial 24 hours after admission, the model performed with an AUC of 0.680 (95% CI: 0.651-0.709) in the primary cohort and an AUC of 0.673 (95% CI: 0.630-0.715) (Supplementary Table 2).

Discussion

AKI is a complicated clinical syndrome characterized by reduced urine production and/or rapid increases in serum creatinine[15]. AKI has been reported to be positively associated with short-term mortality in CSRU populations[5 16]. Delayed diagnosis of AKI is an independent risk factor for nosocomial death[17]. Therefore, the early identification of patients at risk for AKI might help to reduce short-term mortality, improve prognosis, and reduce the health care burden.

In this study, we extracted the clinical information of 6271 patients from the MIMIC-III database. We identified the following 14 possible risk factors for severe AKI by LASSO regression and logistical regression: age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO_2, sedative use, furosemide, atrial fibrillation, congestive heart failure, and left heart catheterization. Subsequently, a clinical score model was constructed by quantifying the weight of the aforementioned variables. The clinical score model was well fitted, as evaluated by the AUC, calibration curves and decision curve analysis in both the primary and validation cohorts. The model could calculate a severe AKI probability immediately after the initial 24 hours and might help clinicians perform early intervention.

Several scoring systems and prognostic models have been built to predict AKI. Scoring systems such as the Cleveland Clinic Score[18] and the Mehta Score[19] only consider AKI patients requiring dialysis and thus might miss patients with subclinical AKI. Additionally, clinical

prediction models have been used to forecast AKI in patients undergoing cardiac surgery[9] or coronary angiography[20]. These studies enrolled both mild and severe AKI patients. Our model was generated from the MIMIC-III database, with a larger sample size and more variables. This study predicted only severe AKI, which might be more attractive for clinical practice. Moreover, the primary cohort and validation cohort were assigned by admission time. According to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement, nonrandom assignment by time is a stronger design feature for evaluating model performance than random assignment[21].

LASSO regression is a popular variable selection algorithm for multicollinear data or high-dimensional data[22]. LASSO has been widely used for clinical prediction. For example, via LASSO, researchers have built a clinical model to predict the diagnosis and prognosis of colon cancer[23]. A radiomics signature using LASSO has been developed to evaluate survival in patients with non-small-cell lung cancer[24]. LASSO has been used to predict AKI in patients with hematologic tumors, patients suffering from cardiac surgery or patients hospitalized in the neurosurgical intensive care unit[12 22 25]. In the present study, based on clinical profiles, LASSO was performed to select relevant coefficients from a multitude of variables, simultaneously removing all unrelated variables. Through dimensionality reduction using LASSO, 42 clinical variables were screened down to 14 risk factors, according to the 1 − standard error criterion.

Among those 14 variables, older age and obesity were independent risk factors for AKI, as indicated by previous investigations[26 27]. Additionally, hypotension has been reported to be associated with new-onset AKI in ICU patients with shock[28]. High CVP, indicating fluid overload, is another factor affecting AKI[29]. Consistent with previous studies, these risk factors

were included in the clinical score model and given a weighted score. Reduced urine output is a clinical manifestation of AKI and is also an important factor underlying the poor prognosis of AKI. In this study, decreased urine output was one of the most important predictors of AKI in CSRU patients. Overall, the clinical score model contained 14 variables, more than half of which have been reported to be associated with AKI. In addition, ROC curves, calibration curves, and decision curve analysis showed consistent results in both the primary and validation cohorts, showing that the clinical score model could be an effective and reliable tool for predicting the risk of severe AKI.

Several limitations of our study must be noted. First, this study was based on the MIMIC-III database, whose data were collected between 2001 and 2012. Some therapies might not meet the latest guidelines and some newer medicines might not be included. Because of the single-center nature of the data, the performance of our model might vary when applied to other regions. The potential residual confounding by variables not recorded in this database could not be evaluated. Second, only patients without existing renal failure were included in this study. Thus, this novel score model might not be suitable for those with a renal failure history. Third, missing values were filled by the random forest method, which might lead to biased regression coefficient estimates[30]. Therefore, further studies are needed to verify our model. Fourth, our model was designed to be used immediately after the initial 24 hours of admission, and it may not work for patients who suffer AKI within those initial 24 hours.

Conclusion

In conclusion, this study established and validated a novel clinical score by using LASSO

regression and logistic regression to screen for multiple clinical risk factors to estimate the probability of severe AKI in CSRU patients. This clinical score model can be an intuitive and reliable predictive tool that might help in individualized clinical decision-making and risk management for severe AKI.

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Contributors TH: Conceptualization, data analysis, writing original draft, writing review and editing. WH: Conceptualization, writing original draft, writing review and editing. YX, WL and YL: Writing original draft and data curation. HL, JJH and JPH: Literature search and data interpretation. YC: Literature search and data interpretation. QG: Conceptualization, writing review and editing, and data curation. JW: Conceptualization, writing review and editing, and data curation.

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Competing interests None declared.

Patient consent for publication Not required.

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Data availability statement The dataset analyzed to generate the findings for this study is available from the corresponding author on reasonable request.

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Table 1 Baseline characteristics of the enrolled subjects in the primary and validation cohorts.

	Primary cohort	Validation cohort	*P*
n	4388	1883	
Age, years	66.0±12.8	65.9±13.3	0.715
Male	2921 (66.6)	1229 (65.3)	0.332
Weight, kg	83.0±19.1	83.2±20.0	0.785
Heart rate, /min	84.9±10.7	84.6±10.8	0.357
Respiratory rate, /min	17.2±3.1	17.2±3.0	0.914
Glucose, mg/dL	131.2±23.2	132.4±23.2	0.060
SBP, mmHg	113.3±10.7	113.9±10.8	0.040
DBP, mmHg	57.1±6.9	57.3±7.0	0.244
CVP, mmHg	10.6±3.5	10.7±3.6	0.191
Urine output, mL	2075.0 (1480.0-2880.0)	2080.0 (1457.0-2900.0)	0.949
pO_2, mmHg	314.0 (211.0-383.0)	308.0 (206.0-386.0)	0.168
Sedative	3707 (84.5)	1593 (84.6)	0.905
Ventilation	3836 (87.4)	1642 (87.2)	0.811
Furosemide	675 (15.4)	292 (15.5)	0.901
Atrial fibrillation	1695 (38.6)	754 (40.0)	0.293
Congestive heart failure	1018 (23.2)	442 (23.5)	0.814
Stroke	258 (5.9)	108 (5.7)	0.823
Left heart catheterization	1288 (29.4)	551 (29.3)	0.942
Severe AKI	2452 (55.9)	1020 (54.2)	0.213

The data are depicted as the mean ± standard deviation, the median (interquartile range) or a number (percentage). Continuous data were compared with Student's t test or the rank-sum test, while categorical data were compared using the chi-square test. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; pO_2, partial pressure of oxygen;

AKI, acute kidney injury.

Table 2 Baseline characteristics of the severe AKI and non-severe AKI groups in the primary cohort.

	Severe AKI	Non-severe AKI	*P*
n	2452	1936	
Age, years	67.4±12.2	64.3±13.3	<0.001
Male	1606 (65.5)	1315 (67.9)	0.094
Weight, kg	86.7±20.2	78.4±16.5	<0.001
Heart rate, /min	85.0±10.8	84.7±10.6	0.475
Respiratory rate, /min	17.2±3.1	17.2±3.0	0.999
Glucose, mg/dL	133.4±23.6	128.6±22.2	<0.001
SBP, mmHg	112.7±10.5	114.0±10.8	<0.001
DBP, mmHg	56.5±6.9	57.9±6.9	<0.001
CVP, mmHg	11.2±3.7	9.8±3.1	<0.001
Urine output, mL	1735.5 (1245.0-2384.3)	2550.0 (1930.0-3355.0)	<0.001
pO_2, mmHg	309.0 (204.0-379.0)	323.0 (224.0-389.0)	0.009
Sedative	2116 (86.3)	1591 (82.2)	<0.001
Ventilation	2183 (89.0)	1653 (85.4)	<0.001
Furosemide	341 (13.9)	334 (17.3)	0.002
Atrial fibrillation	1074 (43.8)	621 (32.1)	<0.001
Congestive heart failure	673 (27.4)	345 (17.8)	<0.001
Stroke	132 (5.4)	126 (6.5)	0.121
Left heart catheterization	762 (31.1)	526 (27.2)	0.005

The data are depicted as the mean ± standard deviation, the median (interquartile range) or a number (percentage). Continuous data were compared with Student's t test or the rank-sum test, while categorical data were compared using the chi-square test. SBP, systolic blood pressure;

DBP, diastolic blood pressure; CVP, central venous pressure; pO_2, partial pressure of oxygen; AKI, acute kidney injury.

Table 3 Variables in the LASSO regression and multivariate logistic regression models.

Variables	LASSO	Logistic		
	β	*β*	OR (95% CI)	*P*
Age	0.011221	0.017	1.017 (1.010-1.023)	<0.001
Male	-0.165641	-0.404	0.667 (0.568-0.784)	<0.001
Weight	0.023091	0.031	1.032 (1.027-1.037)	<0.001
Heart rate	0.000058	0.007	1.007 (1.000-1.014)	0.055
Respiratory rate	-0.006347	-0.042	0.959 (0.936-0.982)	0.001
Glucose	0.000846	0.002	1.002 (0.999-1.005)	0.181
SBP	-0.004721	-0.010	0.990 (0.983-0.997)	0.007
DBP	-0.009688	-0.015	0.985 (0.974-0.997)	0.011
CVP	0.063826	0.072	1.075 (1.051-1.099)	<0.001
Urine output	-0.000603	-0.001	0.999 (0.999-0.999)	<0.001
pO_2	-0.000127	-0.001	0.999 (0.998-1.000)	0.001
Sedative	0.173715	0.340	1.405 (1.032-1.912)	0.031
Ventilation	0.093818	0.189	1.209 (0.862-1.694)	0.272
Furosemide	-0.484207	-0.757	0.469 (0.387-0.569)	<0.001
Atrial fibrillation	0.193466	0.279	1.322 (1.139-1.536)	<0.001
Congestive heart failure	0.207495	0.305	1.357 (1.143-1.611)	<0.001
Stroke	-0.021989	-0.254	0.776 (0.580-1.038)	0.087
Left heart catheterization	0.043483	0.166	1.181 (1.014-1.376)	0.033

LASSO, least absolute shrinkage and selection operator; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; pO_2, partial pressure of oxygen.

Table 4 Model performance in the primary and validation cohorts.

	AUC (95% CI)	Accuracy (95% CI)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Cutoff value	Cutoff score
Primary cohort	0.779 (0.766-0.793)	0.702 (0.688-0.715)	0.609	0.820	0.811	0.623	0.566	167.9
Validation cohort	0.778 (0.757-0.799)	0.715 (0.694-0.735)	0.781	0.637	0.718	0.722	0.065	161.8

AUC, area under the receiver operating characteristic curve; CI, confidence interval.

Figure legends

Figure 1 Flow chart of enrolled subjects.

A total of 6271 CSRU stay records were enrolled in this study. ICU, intensive care unit; CSRU, cardiac surgery recovery unit.

Figure 2 LASSO coefficient profiles of variables and misclassification errors for different models.

The upper panel presents the associations between the coefficients of variables and the log lambda value. Each line corresponds to one distinct variable. With increasing log lambda, the coefficient of the variable tended toward 0. The lower panel presents the selection of the applicable model. Vertical lines were drawn at the optimal values by adopting the minimum criteria (dashed line) and the SE of the minimum criteria (dotted line, the 1 − SE criteria). In our study, the lambda value was chosen according to the 1 − SE criteria. LASSO, least absolute shrinkage and selection operator; SE, standard error.

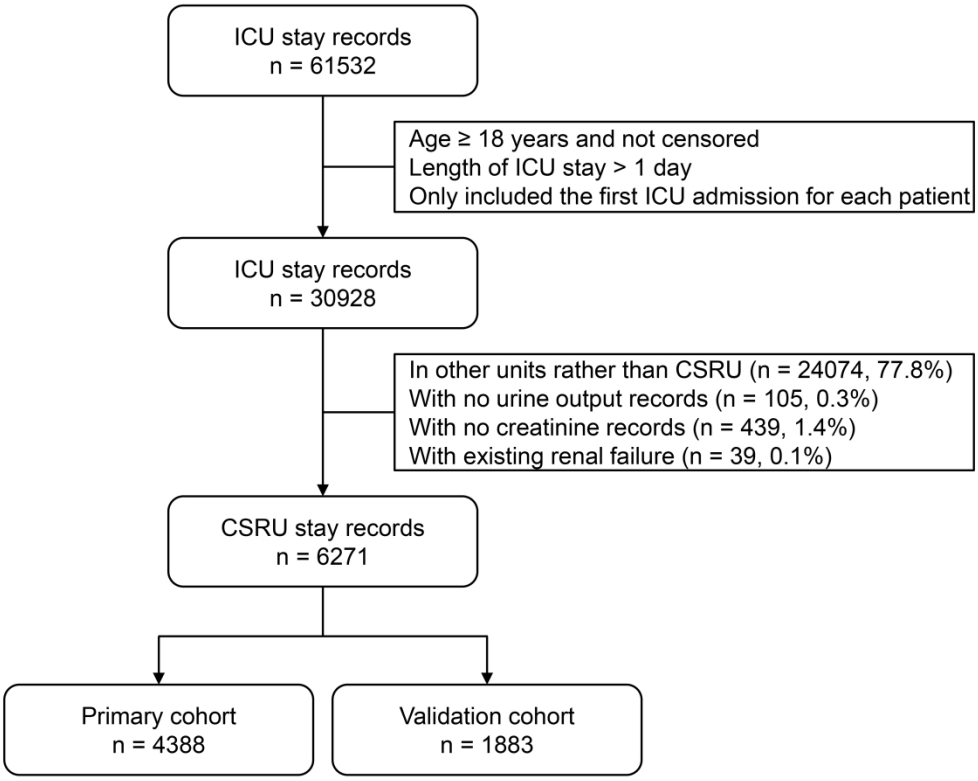
Figure 3 Clinical score for the prediction of severe AKI in CSRU patients.

All 14 selected variables, including age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO_2, sedative usage, furosemide, atrial fibrillation, congestive heart failure and left heart catheterization, were given corresponding points based on their values. The total points of these variables corresponded to the predicted probability of severe AKI in the CSRU. SBP, systolic

blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit.

Figure 4 Performance evaluation of the severe AKI prediction model.

ROC curves in the primary cohort (A) and validation cohort (B). The AUCs of the model in the primary and validation cohorts were 0.779 and 0.778, respectively. Calibration curves in the primary cohort (C) and validation cohort (D). The observed values were close to the ideal values, indicating a satisfactory forecasting performance of the clinical score model. Decision curve analyses in the primary cohort (E) and validation cohort (F), showing the net benefit from the model. AKI, acute kidney failure; ROC, receiver operator characteristic curve; AUC, area under the receiver operating characteristic curve.



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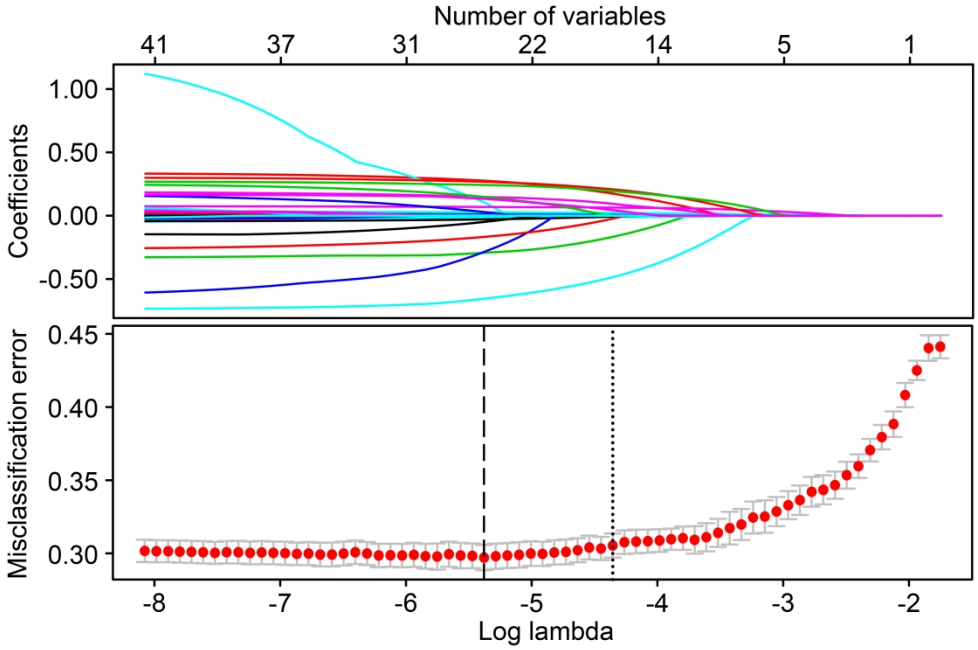

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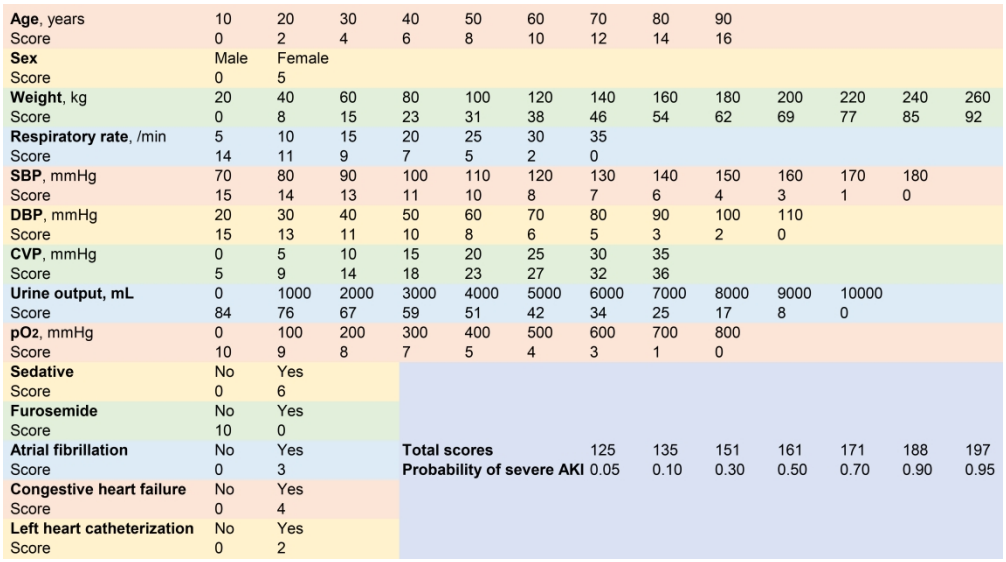

Age, years	10	20	30	40	50	60	70	80	90				
Score	0	2	4	6	8	10	12	14	16				
Sex	Male	Female											
Score	0	5											
Weight, kg	20	40	60	80	100	120	140	160	180	200	220	240	260
Score	0	8	15	23	31	38	46	54	62	69	77	85	92
Respiratory rate, /min	5	10	15	20	25	30	35						
Score	14	11	9	7	5	2	0						
SBP, mmHg	70	80	90	100	110	120	130	140	150	160	170	180	
Score	15	14	13	11	10	8	7	6	4	3	1	0	
DBP, mmHg	20	30	40	50	60	70	80	90	100	110			
Score	15	13	11	10	8	6	5	3	2	0			
CVP, mmHg	0	5	10	15	20	25	30	35					
Score	5	9	14	18	23	27	32	36					
Urine output, mL	0	1000	2000	3000	4000	5000	6000	7000	8000	9000	10000		
Score	84	76	67	59	51	42	34	25	17	8	0		
pO2, mmHg	0	100	200	300	400	500	600	700	800				
Score	10	9	8	7	5	4	3	1	0				
Sedative	No	Yes											
Score	0	6											
Furosemide	No	Yes											
Score	10	0											
Atrial fibrillation	No	Yes		**Total scores**			125	135	151	161	171	188	197
Score	0	3		**Probability of severe AKI**			0.05	0.10	0.30	0.50	0.70	0.90	0.95
Congestive heart failure	No	Yes											
Score	0	4											
Left heart catheterization	No	Yes											
Score	0	2											

Figure 3 Clinical score for the prediction of severe AKI in CSRU patients.
All 14 selected variables, including age, sex, weight, respiratory rate, SBP, DBP, CVP, urine output, pO2, sedative usage, furosemide, atrial fibrillation, congestive heart failure and left heart catheterization, were given corresponding points based on their values. The total points of these variables corresponded to the predicted probability of severe AKI in the CSRU. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVP, central venous pressure; AKI, acute kidney injury; CSRU, cardiac surgery recovery unit.

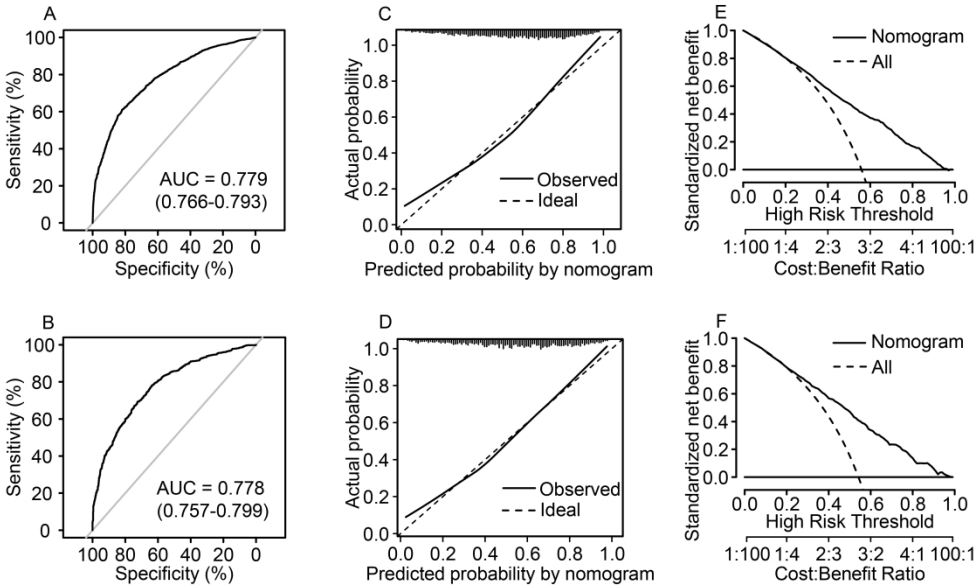

Figure 4 Performance evaluation of the severe AKI prediction model.
ROC curves in the primary cohort (A) and validation cohort (B). The AUCs of the model in the primary and validation cohorts were 0.779 and 0.778, respectively. Calibration curves in the primary cohort (C) and validation cohort (D). The observed values were close to the ideal values, indicating a satisfactory forecasting performance of the clinical score model. Decision curve analyses in the primary cohort (E) and validation cohort (F), showing the net benefit from the model. AKI, acute kidney failure; ROC, receiver operator characteristic curve; AUC, area under the receiver operating characteristic curve.

Supplementary tables

Supplementary Table 1 Performance evaluation of the model without urine output.

	AUC (95% CI)	Accuracy (95% CI)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Cutoff value	Cutoff score
Primary cohort (n=4388)	0.713 (0.698-0.728)	0.658 (0.644-0.672)	0.594	0.739	0.743	0.590	0.363	97.2
Validation cohort (n=1883)	0.718 (0.695-0.741)	0.666 (0.644-0.687)	0.712	0.610	0.683	0.642	0.095	94.1

AUC, area under the receiver operating characteristic curve; CI, confidence interval.

Supplementary Table 2 Model performance in patients without suffering AKI in the initial 24 hours.

	AUC (95% CI)	Accuracy (95% CI)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Cutoff value	Cutoff score
Primary cohort (n=1800)	0.680 (0.651-0.709)	0.704 (0.682-0.725)	0.538	0.757	0.412	0.838	-0.943	149.6
Validation cohort (n=820)	0.673 (0.630-0.715)	0.637 (0.603-0.670)	0.624	0.641	0.343	0.850	-1.124	147.4

AUC, area under the receiver operating characteristic curve; CI, confidence interval.

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2-3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	D;V	Describe eligibility criteria for participants.	5
	5c	D;V	Give details of treatments received, if relevant.	5
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5-6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	5-6
Sample size	8	D;V	Explain how the study size was arrived at.	5
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	6
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	6
	10c	V	For validation, describe how the predictions were calculated.	6
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	6
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	6
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	6
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	7
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	7
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	7
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	8
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	8
	15b	D	Explain how to the use the prediction model.	8
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	8
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	8
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	11
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	10
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	9-10
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	9
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	12
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	12

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.