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ORIGINAL RESEARCH

Prediction of Acute Kidney Injury for Critically Ill Cardiogenic Shock Patients with Machine Learning Algorithms

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Background: The aim of this study was to use five machine learning approaches and logistic regression to design and validate the acute kidney injury (AKI) prediction model for critically ill individuals with cardiogenic shock (CS).

Methods: All patients who diagnosed with CS from the MIMIC-IV database, the eICU database, and Zhongnan hospital of Wuhan university were included in this study. Clinical information, including demographics, comorbidities, vital signs, critical illness scores and laboratory tests was retrospectively collected. Five machine learning algorithms (LightGBM, decision tree, XGBoost, random forest, and ensemble model) and one conventional logistic regression were applied for the prediction of AKI in critically ill individuals with CS. ROC curves were generated via python software to assess the overall performance of machine learning algorithms and the SHAP analysis was adopted to reveal the impact of prediction for each feature.

Results: The ensemble model exhibited the best predictive ability (AUC:0.91, 95% CI, 0.88–0.94), followed by random forest (AUC:0.90, 95% CI, 0.86–0.94) and XGBoost (AUC:0.89, 95% CI, 0.84–0.92). While the logistic regression model obtained the worst predictive performance (AUC:0.62, 95% CI, 0.56–0.68). When validated the prediction models with eICU database, the ensemble model exhibited the best predictive ability (AUC:0.92, 95% CI, 0.89–0.96), while the logistic model obtained the worst predictive performance (AUC:0.61, 95% CI, 0.56–0.67). Finally, we verified the prediction models using the data from our hospital and ensemble model still exhibited the best predictive ability (AUC:0.74, 95% CI, 0.62–0.86), while the decision tree model obtained the worst predictive performance (AUC:0.52, 95% CI 0.35–0.70).

Conclusion: Machine learning algorithms could be utilized for the AKI prediction among critically ill CS patients, and exhibit superior predictive performance compared to the conventional logistic regression analysis.

Keywords: cardiogenic shock, acute kidney injury, MIMIC database, prediction model, machine learning

Introduction

Cardiogenic shock (CS), renowned by an unexplainedly rapid drop in cardiac output that leads to hypotension and indications or symptoms of hypoperfusion, is a life-threatening condition that requires immediate pharmacological and/or mechanical intervention.[1,2] Despite significant advances in their pathogenesis, diagnosis, and treatment, CS patients continue to be associated with a high rate of morbidity and death, as well as longer hospital stays and expensive medical healthcare costs.[3–6] Additionally, acute kidney injury (AKI) in the context of CS, also treated as type 1 cardiorenal syndrome, is increasing in the risk of adverse clinical outcomes and appears to be predictive risk factor for the prognosis

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of CS patients.[7–10] Therefore, doctors must prioritize identifying patients at high risk of AKI using biomarkers or prediction algorithms in order to manage these patients effectively.

Numerous prediction models of AKI had been created and validated in earlier research using a variety of methods, including logistic regressions, LASSO regressions, extreme gradient boosting (XGBoost), and random forest.[11–14] However, many of them were logistic regression, which needed independent features based on statistical significance for multiple regression models, and certain variables may have been omitted if they were not statistically significant while having causal impacts on outcomes. Additionally, the precise significance of each clinical trait that may assist doctors in identifying individuals at high risk of AKI has not been investigated before. Thus, in the present work, we explored the accuracy of gradient boosting decision tree algorithms for developing AKI models in CS patients admitted to the intensive care unit using a big clinical database, and we also used another public database and our hospital to corroborate these results. Additionally, SHAP analysis was employed to provide in-depth explanations for their quantitative effects on production.

Materials and Methods

Data Source

This was a two-step analysis; we built the AKI prediction models based on the MIMIC database, and then externally confirmed the prediction models with eICU database and Zhongnan hospital of Wuhan university. Clinical data for all CS patients in this study were extracted from two large critical care databases in the United States of America, namely the MIMIC IV v1.0 and the eICU-CRD v2.0.[15,16] After successfully completing their training and assessment, our team was granted access to extract data from this database; informed consent was waived in this case since all patients in this database were de-identified. Moreover, adult patients admitted to the CCU at Zhongnan Hospital of Wuhan University from January 1, 2014, to June 1, 2015, as previously described,[17] were also included in this study as the external validation cohort. This study was reviewed and approved by the clinical research ethics committee of Zhongnan hospital of Wuhan university.

Selection of Participants

The research included patients admitted to intensive care units (ICUs) who were diagnosed with CS using an International Classification of Diseases (ICD) code. Additionally, we eliminated patients with repeated ICU hospitalizations, hospital stays of less than 48 hours, and patients with missing clinical data (variables with a missing value rate of greater than 20%). Additionally, the research excluded participants with a history of end-stage renal disease (ESRD). Finally, a total of 2615 patients (1224 were in the MIMIC-IV database and 1225 were in the eICU database, and 166 were in our hospital) were enrolled in this retrospective study (Figure 1) and were assigned as training set (MIMIC database, n = 1224) and validation set (eICU database, n = 1225). Moreover, patients in our hospital were appointed as external validation cohort (n = 166).

Variable Extraction

Age, gender, BMI, ethnicity (white, black, and other or unknown), commodities, severity ratings, treatments, prescriptions, vital signs, and laboratory results were collected from these two databases using PostgreSQL 9.6's structured query language. The CKD-EPI algorithm was used to determine the estimated glomerular filtration rate (eGFR) based on the initial serum creatinine values.[18] To capture the statistical information of numeric variables, the initial, minimum, mean, and maximum values of vital signs and laboratory findings in the first 48 hours of their ICU admission were calculated as extra statistical values and included in the feature set. Due to the bias, which may produce by the missing data, variables having >70% missing values were omitted from further analysis. Other variables with a lesser degree missing data were evaluated using multiple imputation approach. Finally, a total of 128 characteristics were gathered.

The primary outcome in this study was the incidence of CS-AKI according to the KDIGO-AKI criteria based on serum creatinine in the first 48 hours of their ICU admission.[18]

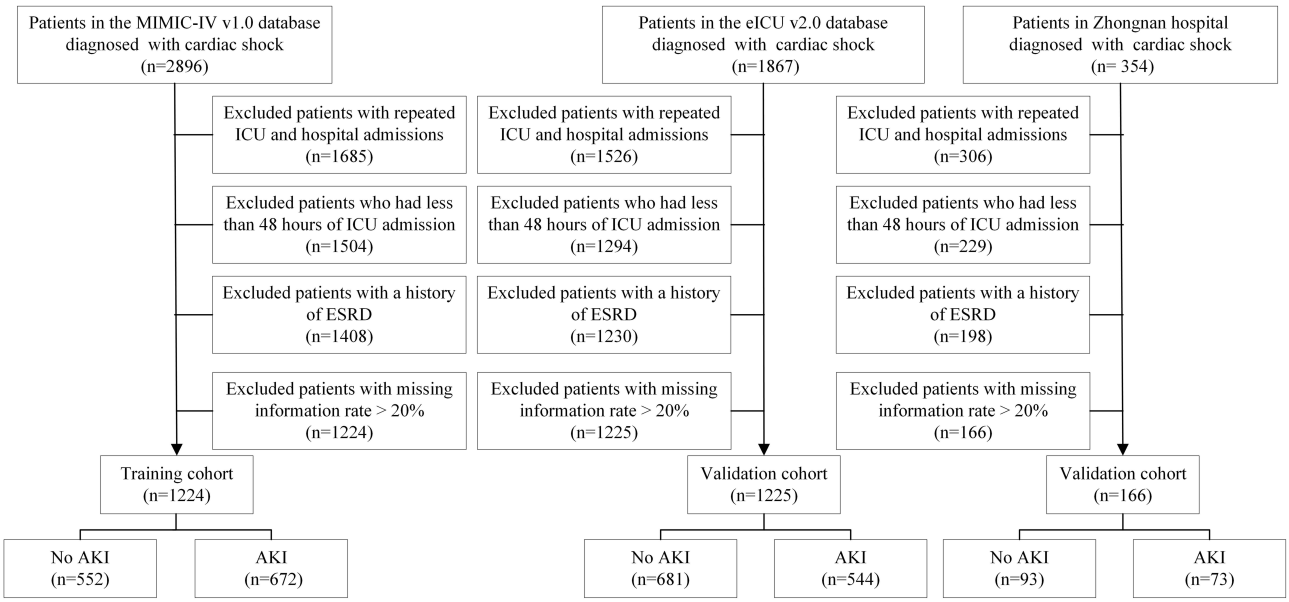

Figure 1 The flow chart of this study.

Statistical Analysis

The mean (standard deviation) of continuous variables was provided, whereas categorical covariates were presented as a number (percentage). To create prediction models, logistic regression, random forest, and two gradient boosting decision trees, namely LightGBM and XGBoost, were used and the parameters of these machine learning models were reported in the Supplemental Table 2. Additionally, an ensemble model was created to boost prediction performance, using the staking strategies of random forest, LightGBM, and XGBoost. The prediction probabilities of the three models were fed into a logistic regression model to give a final prediction. In the training step, a ten-fold cross-validation was utilized to evaluate the performance and get the ideal control settings for each method. Additionally, four measures were used to evaluate predictor performance: accuracy, recall, F1 value, and area under the curve (AUC). To evaluate the positive or negative influence of the significant characteristics revealed for AKI prediction and the connection between them, a shapley additive explanations (SHAP) analysis was performed using Python 3.7.0. The SHAP value represents the anticipated value given to each feature in the data.

Results

Study Cohorts and Baseline Characteristics

We eventually recruited 1224 cases of critically ill people with CS from MIMIC cohort, 1225 cases from eICU cohort, and 166 cases from our hospital. The mean age of included cases was 69.6 ± 14.4 years old in the MIMIC cohort, 66.2 ± 14.2 years old in the eICU cohort, and 66.3 ± 14.7 years old in our hospital. The proportion of male patients was 69.5%, 61.5%, and 56.6% in the MIMIC dataset, eICU dataset, and our hospital, respectively. As for CS-AKI, the rate was 54.9% in the MIMIC cohort, 44.4% in the eICU cohort, and 44.0% in our hospital. The detailed comparisons of clinical data among the three cohorts were listed in Table 1 and Supplemental Table 1.

Performance Evaluation of Six Models

We used the 5 machine learning models and one conventional logistic regression model to select the most informative metrics associated with CS-AKI for critically ill individuals in the MIMIC cohort. We generated ROC curves to objectively assess the overall performance of prediction models. As shown in Figure 2A, the ensemble model exhibited the best predictive ability (AUC:0.90, 95% CI, 0.88–0.94), followed by random forest (AUC:0.90, 95% CI, 0.86–0.94) and XGBoost (AUC:0.89, 95% CI, 0.84–0.92). While the logistic regression model obtained the worst predictive

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Table 1 Comparisons of Baseline Characteristics in All Cohorts

Characteristics	Training Set (n=1224)	Validation Set (n=1225)	External Validation Set (n=166)	P value
Age, years old	69.6 ± 14.4	66.2 ± 14.2	66.3 ± 14.7	<0.001
Gender, male, n (%)	729 (59.6)	472 (38.5)	94 (56.6)	<0.001
BMI, kg/m^2	28.9 ± 6.5	29.3 ± 7.3	23.7 ± 3.4	<0.001
Ethnicity, n (%)				<0.001
White	793 (64.8)	1003 (81.9)	0 (0.0)	
Black	118 (9.6)	132 (10.8)	0 (0.0)	
Others	313 (25.6)	90 (7.3)	166 (100.0)	
Intervention, n (%)				
MV	855 (69.9)	681 (55.6)	113 (68.1)	<0.001
Vasopressors	1032 (84.3)	824 (67.3)	138 (83.1)	<0.001
RRT	157 (12.8)	119 (9.7)	15 (9.0)	0.034
Comorbidities, n (%)				
Congestive heart failure	955 (78.0)	390 (31.8)	10 (6.0)	<0.001
Hypertension	520 (42.5)	648 (52.9)	108 (65.1)	<0.001
Diabetes	410 (33.5)	403 (32.9)	44 (26.5)	0.196
Chronic kidney disease	358 (29.2)	179 (14.6)	28 (16.9)	<0.001
COPD	357 (29.2)	197 (16.1)	47 (28.3)	<0.001
Liver disease	193 (15.8)	18 (1.5)	30 (18.1)	<0.001
CCI, points	6.8 ± 2.6	4.2 ± 2.1	7.0 ± 2.6	<0.001
Drugs usage, n (%)				
ACEI/ARB	548 (44.8)	504 (41.1)	73 (44.9)	0.187
β blockers	920 (75.2)	644 (52.6)	87 (52.4)	<0.001
CCB	169 (13.8)	158 (12.9)	24 (14.5)	0.741
Diuretic	1098 (89.7)	720 (58.8)	70 (42.2)	<0.001
Statin	799 (65.3)	685 (55.9)	101 (60.8)	<0.001
Aspirin	971 (79.3)	602 (49.1)	99 (59.6)	<0.001
PPI	759 (62.0)	464 (37.9)	101 (60.8)	<0.001
Score system, points				
SOFA	8.8 ± 4.0	6.8 ± 3.1	5.8 ± 2.0	<0.001
OASIS	38.4 ± 9.8	30.5 ± 11.1	–	<0.001
APSIII	66.0 ± 27.9	66.7 ± 30.2	–	0.510
Vital signs				
SBP_first, mmHg	112.5 ± 22.1	113.0 ± 26.3	112.1 ± 22.2	0.852
DBP_first, mmHg	66.3 ± 19.3	66.7 ± 18.7	64.7 ± 19.1	0.444
MAP_first, mmHg	80.5 ± 19.6	87.9 ± 26.6	79.8 ± 18.4	<0.001
Heart rate_first, bpm	92.1 ± 21.8	93.4 ± 23.2	90.9 ± 21.1	0.727
RR_first, bpm	20.9 ± 6.5	20.3 ± 5.8	20.8 ± 6.7	0.028
SpO_2_first, %	96.1 ± 5.1	95.4 ± 6.4	95.7 ± 4.9	0.027
Laboratory values				
WBC_first, × 10^9/L	17.1 ± 9.0	12.9 ± 7.3	16.3 ± 6.7	<0.001
Hemoglobin_first, g/dL	10.3 ± 2.5	12.2 ± 2.5	10.6 ± 2.4	<0.001
Platelet_first, × 10^9/L	177.9 ± 92.2	216.3 ± 89.4	179.7 ± 94.7	<0.001
Hematocrit_first, %	35.7 ± 7.1	37.2 ± 7.3	36.1 ± 6.9	<0.001
RBC_first, × 10^{12}/L	4.1 ± 0.8	4.1 ± 0.8	4.1 ± 0.8	0.364
RDW_first, %	15.4 ± 2.3	15.3 ± 2.3	15.5 ± 2.7	0.292
ALT_first, U/L	254.1 ± 80.1	101.1 ± 43.1	245.6 ± 69.8	<0.001
AST_first, U/L	387.3 ± 97.3	155.5 ± 59.2	339.4 ± 86.7	<0.001
Albumin_first, g/dL	3.2 ± 0.5	3.1 ± 0.6	3.2 ± 0.5	<0.001
Bilirubin_first, mmol/L	1.1 ± 0.3	1.2 ± 0.4	1.1 ± 0.3	0.694
Anion gap_first, mEq/L	19.2 ± 5.2	12.6 ± 4.7	18.9 ± 4.8	<0.001

(*Continued*)

Table 1 (Continued).

Characteristics	Training Set (n=1224)	Validation Set (n=1225)	External Validation Set (n=166)	P value
Bicarbonate_first, mEq/L	23.2 ± 4.3	23.1 ± 5.0	23.7 ± 4.2	0.266
Glucose_first, mg/dL	132.3 ± 40.1	181.4 ± 75.7	131.6 ± 47.6	<0.001
BUN_first, mg/dL	32.2 ± 12.9	28.6 ± 10.4	30.8 ± 12.1	0.547
Creatinine_first, mg/dL	1.5 ± 0.5	1.7 ± 0.7	1.5 ± 0.6	<0.001
Potassium_first, mmol/L	3.9 ± 0.7	4.3 ± 0.9	3.8 ± 0.6	<0.001
Sodium_first, mmol/L	135.6 ± 5.6	136.7 ± 5.6	136.4 ± 5.2	<0.001
PT_first, s	17.7 ± 8.0	16.6 ± 7.5	16.8 ± 8.0	0.044
APTT_first, s	42.8 ± 15.0	36.5 ± 14.8	34.8 ± 12.9	<0.001
Baseline eGFR, mL/m 5.2in	58.3 ± 20.1	52.0 ± 20.9	58.5 ± 19.4	<0.001
CVP, mmHg	15.4 ± 5.1	15.3 ± 6.1	15.0 ± 6.4	0.631
Input of first 48 hours, mL	6984.3 ± 3029.4	11,819.9 ± 4336.5	6758.8 ± 3065.4	<0.001
Output of first 48 hours, mL	4548.5 ±1837.8	9985.7 ± 4315.9	4219.5 ± 1808.3	<0.001
AKI, n (%)	672 (54.9)	544 (44.4)	73 (44.0)	<0.001

Abbreviations: BMI, body mass index; MV, mechanical ventilation; RRT, renal replacement therapy; COPD, chronic obstructive pulmonary disease; CCI, Charlson comorbidity index; ACEI/ARB, Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers; CCB, Calcium calcium blockers; PPI, proton pump inhibitor; SOFA, sequential organ failure assessment; OASIS, oxford acute severity of illness score; APSIII, acute physiology score III; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; RR, respiratory rate; WBC, white blood cell; RBC, red blood cell; RDW, red cell distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time; APTT, activated partial thromboplastin time; eGFR, estimated glomerular filtration rate; CVP, central venous pressure; AKI, acute kidney injury.

performance (AUC:0.62, 95% CI, 0.56–0.68). When validated the prediction models with eICU database (Figure 2B), ensemble model exhibited the best predictive ability (AUC:0.92, 95% CI, 0.89–0.96), while the logistic model obtained the worst predictive performance (AUC:0.61, 95% CI, 0.56–0.67). Finally, we verified the prediction models by using the data from our hospital (Figure 2C), ensemble model still exhibited the best predictive ability (AUC:0.74, 95% CI, 0.62–0.86), while the decision tree model obtained the worst predictive performance (AUC:0.52, 95% CI 0.35–0.70). Other parameters related to predictive models, such as recall value, precision value, and F1 value were exhibited in Table 2.

Analysis of Feature Importance

With respect to clinical explanation in the AKI prediction model, we identified the top 15 clinical features closely associated with AKI among critically ill patients with CS. In the prediction model of random forest (Figure 3A), bilirubin_first, albumin_max, and creatinine_first were the top three features related to CS-AKI. In the prediction model of XGBoost (Figure 3B), creatinine_first, Charlson index, and bilirubin_first were the top three features related to CS-AKI. In the prediction model of lightGBM (Figure 3C), creatinine_first, albumin_min, and hemoglobin_first were the top three features related to CS-AKI. To further explain the prediction model at the feature level, we drew a SHAP summary

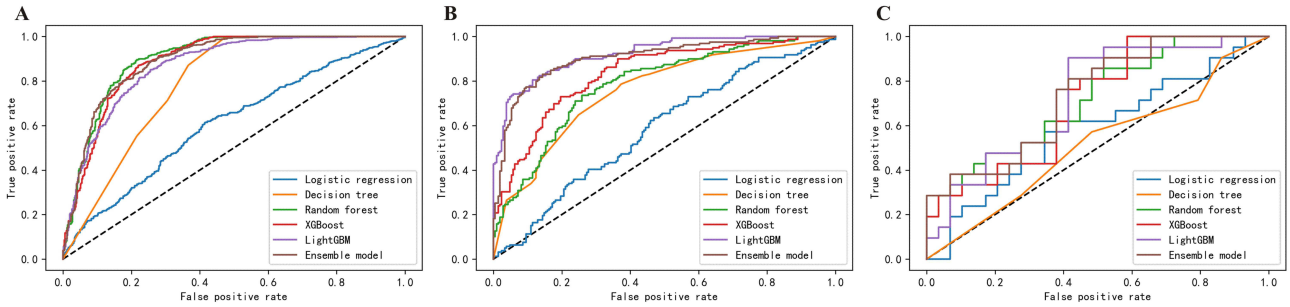

Figure 2 ROC curves of the six prediction models using all features for predicting AKI in MIMIC cohort (**A**), in eICU cohort (**B**), and in Zhongnan cohort (**C**).

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Table 2 Performance of the Prediction Models Using All Features

Model	Accuracy	Recall	F1 score	AUC
Training cohort				
Logistic regression	0.58	0.78	0.60	0.62
Decision tree	0.76	0.87	0.74	0.79
Random forest	0.81	0.84	0.74	0.90
XGBoost	0.81	0.83	0.74	0.89
LightGBM	0.80	0.80	0.77	0.87
Ensemble model	0.81	0.88	0.77	0.91
Validation cohort				
Logistic regression	0.58	0.66	0.61	0.61
Decision tree	0.70	0.79	0.62	0.76
Random forest	0.72	0.63	0.69	0.78
XGBoost	0.76	0.68	0.75	0.83
LightGBM	0.82	0.81	0.80	0.90
Ensemble model	0.84	0.81	0.82	0.92
External validation cohort				
Logistic regression	0.60	0.63	0.55	0.59
Decision tree	0.54	0.57	0.54	0.52
Random forest	0.66	0.61	0.64	0.72
XGBoost	0.68	0.63	0.65	0.71
LightGBM	0.60	0.62	0.60	0.73
Ensemble model	0.64	0.63	0.66	0.74

figure to reveal how top features affect the probability of CS-AKI (Figure 4). Based on SHAP analysis, we used both the direction and strength of each clinical feature to illustrate its impact on the probability of AKI. Take XGBoost for example, a higher level of bilirubin_first, creatinine_first as well as Charlson index were positively associated with the probability of CS-AKI.

Explanation of the XGBoost Model at the Individual Level

We then used the SHAP force figure of significant clinical features to expound the overall impact of crucial features on the AKI predicted by the XGBoost model in individual cases. As illustrated in Figure 5, decremental AKI effects of key features (red) and incremental mortality effects of key features (green) were clearly shown in the SHAP force figure. For example, in case 1 (Figure 5A), the predicted probability for AKI was relatively low due to a series of decremental factors, consisting of a low serum bilirubin_max (0.8mmol/L), low level of ALT_min (316U/L) and APTT_first (82.1s), although this case had lower level of baseline eGFR (10.2mL/min), ALB_mean (2.9g/dL) and high level of APTT_mean (92.8s). However, in case 2 (Figure 5B), the predicted probability for AKI was relatively high due to a list of incremental

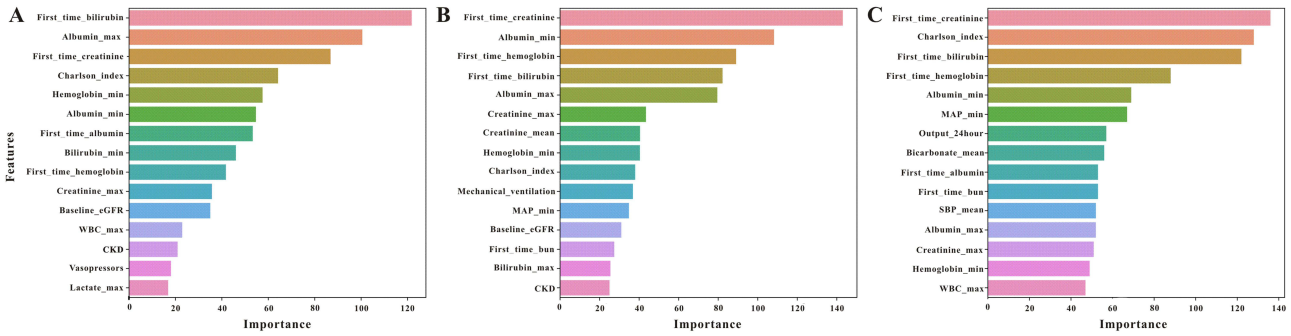

Figure 3 The top 15 features derived from the random forest (**A**), XGBoost (**B**), and lightGBM model (**C**).

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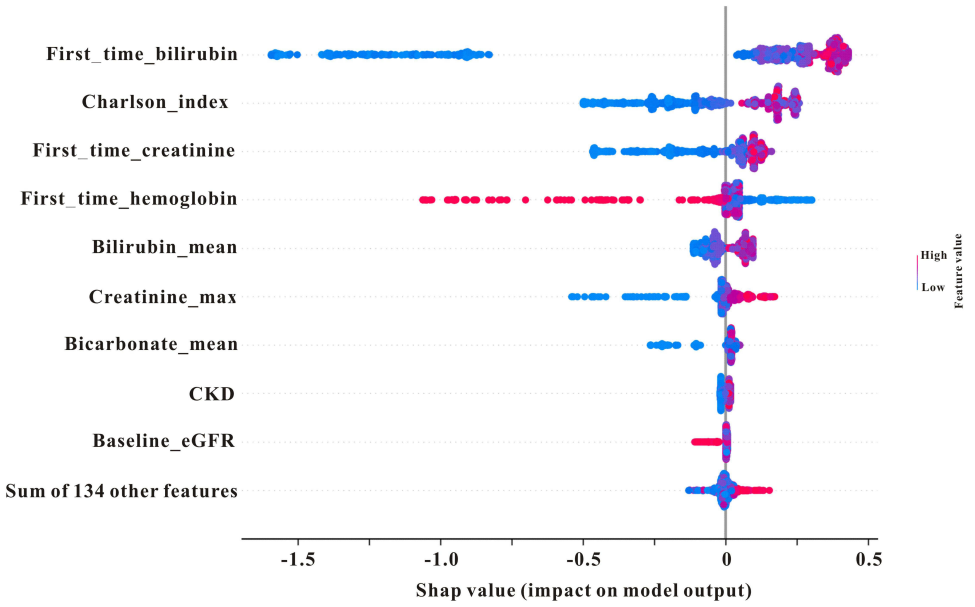

Figure 4 SHAP summary plot of the features of the XGBoost model. The higher the SHAP value of a feature, the higher the probability of AKI. Red represents higher feature values, and blue represents lower feature values.

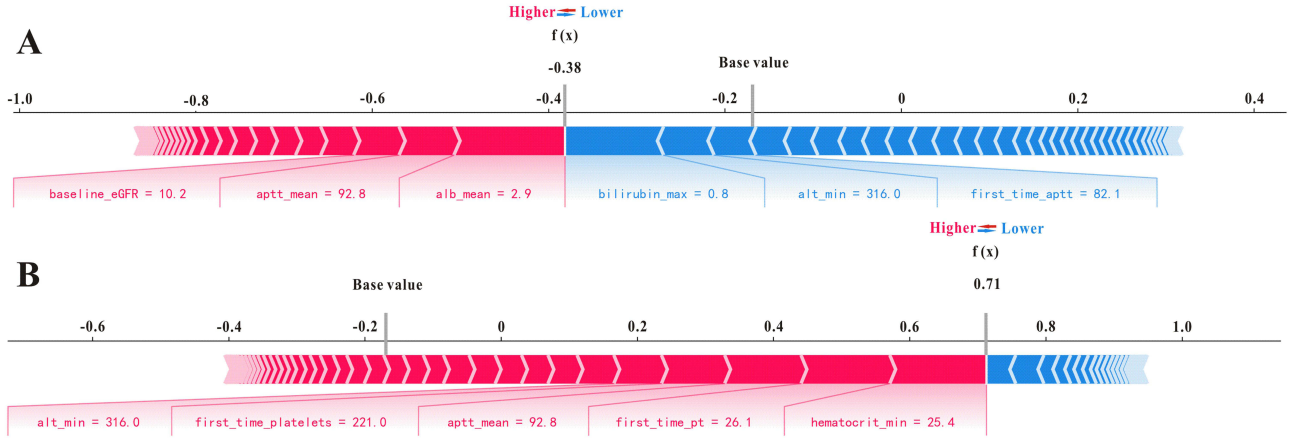

Figure 5 The two representative SHAP force plots of a no-AKI (**A**) and AKI (**B**) patient.

factors, consisting of higher levels of ALT_min (316U/L), platelet_first (221×10^9/L), APTT_mean (92.8s), PT_first (26.1s), hematocrit_min (25.4%).

Discussion

Based on the two ICU databases and the data from our hospital, we applied five machine learning approaches (ie, random forest, decision tree, XGBoost, light GBM, and ensemble model) to accurately predict the AKI for critically ill CS patients. The five machine learning algorithms not only show good performance for the prediction of AKI among critically ill individuals with CS in the eICU cohort but also validated well in the MIMIC-IV database and our hospital. When comparing the predictive accuracy of five machine learning algorithms with the conventional model (logistic regression), the machine learning algorithms obtained superior performance. So far as we know, this is the first clinical investigation to systematically detect the utility of five machine learning models for the prediction of AKI for critically ill CS patients based on relatively larger sample size.

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AKI is one of the most familiar and portentous markers of adverse events for patients with CS and the incidence rate of CS-AKI ranges from 13.0% to 60.4% in previous studies.[10] Compared with those studies, the overall incidence of CS-AKI was 48.6% in this study, which was in conformity to previous study, and the difference of the morbidity in different studies might partly demonstrated by differences in the composition of patients and severity of disease. Furthermore, considering that AKI could independently exacerbate the prognosis of CS patients, a novel biomarker or predicting model, which could exactly recognize patients at high risk of CS-AKI earlier might result in better outcomes and lower hospital care cost.

Machine learning models, in which computers learn to identify their decision-making algorithms, are widely applied in the early diagnosis and prognostic evaluation of CS patients.[19,20] The high capacity of machine learning algorithms depends on their ability to abstract significant metrics from millions of data and complex associations, and thus automatically make classifications.[21] Among the current machine learning approaches, random forest, decision tree, XGBoost, lightGBM, and, ensemble models have been proved to be the appropriate variable selection methods for enormous clinical data. The most obvious advantage of machine learning approaches is that it has favorable power with better stability in a selection of significant metrics while just requiring a much shorter computation time, which is very appropriate to deal with large datasets.[22] In our study, we simultaneously mined two large ICU databases (MIMIC-IV and eICU). With the large sample size and too many clinical variables, machine learning approaches are the best way to select significant survival factors for critically ill CS patients. Importantly, all the machine learning approaches got a nice performance for the AKI prediction of critically ill CS patients.

In our analysis, we found that all the accuracy of machine learning algorithms were much higher than the conventional model (logistic regression) for the prediction of AKI among critically ill CS patients. We believe that the following reasons may at least partly explain this phenomenon. First, our machine learning algorithms are good at dealing with high-order associations between the predictive factors and non-linear relationships for different outcomes. Subsequently, overfitting in logistic regression is sometimes inevitable, while modern machine learning algorithms utilize various rigorous approaches, such as cross-validation, dropout, and regularization, to ultimately avoid overfitting. Based on our analysis, we could conclude that machine learning algorithms are superior to the conventional logistic regression for the AKI prediction of critically ill AKI patients. Moreover, the heterogeneity of the study population should be acknowledged so that future work are needed to explore how subgroups of patients could have different results or conclusions.

The strength of this study was the successful application of machine learning models to predict the AKI of critically ill CS patients based on two large datasets from multiple hospitals across the USA, and confirmed the predictive accuracy with our hospital data. Our analysis reinforces that machine learning algorithms could be adapted to improve the AKI prediction for critically ill CS patients. However, there were still some limitations in this retrospective study. First, the predictive accuracy of machine learning models was good, but not so excellent, especially when we validated those machine learning models in our hospital. Then, the sample size of external validation was relatively small (N = 166). Thirdly, due to the database limited, some important risk factors had a lot of missing value or did not obtain in this study. In addition, the diagnosis of CS was only based on the ICD code, AKI could occur before or concurrently with CS, thus, these prediction models might not always be in advance. Moreover, there were many factors related to AKI being identified in the models; however, their causal relationship is largely unknown, which might have significant impact on clinical management. Finally, we assessed AKI based on the creatinine only for the first 48 hours of their ICU admission. However, most of AKI in ICU patients developed within the first 24 hours,[23] and in this study more than half of patients occurred AKI within the first day of their ICU admission. Hence, this was a retrospective multi-center study, despite validation in another big database and our hospital, more prospective multi-center studies are still proposed to further verify our findings.

Conclusions

Our study revealed that machine learning algorithms could be used for the AKI prediction of critically ill CS patients and exhibit superior predictive performance compared to the conventional logistic regression model.

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki and its later amendments and this study was also approved by the Ethics Committee of the Zhongnan hospital of Wuhan university and given that this was a retrospective observational study and all the data of the patients were de-identified, the informed consent was waived.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval for the version to be published; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declared that there is no conflict of interest.

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