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ORIGINAL RESEARCH

Classification and Regression Tree Predictive Model for Acute Kidney Injury in Traumatic Brain Injury Patients

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Background: Acute kidney injury (AKI) is prevalent in hospitalized patients with traumatic brain injury (TBI), and increases the risk of poor outcomes. We designed this study to develop a visual and convenient decision-tree-based model for predicting AKI in TBI patients.

Methods: A total of 376 patients admitted to the emergency department of the West China Hospital for TBI between January 2015 and June 2019 were included. Demographic information, vital signs on admission, laboratory test results, radiological signs, surgical options, and medications were recorded as variables. AKI was confirmed since the second day after admission, based on the Kidney Disease Improving Global Outcomes criteria. We constructed two predictive models for AKI using least absolute shrinkage and selection operator (LASSO) regression and classification and regression tree (CART), respectively. Receiver operating characteristic (ROC) curves of these two predictive models were drawn, and the area under the ROC curve (AUC) was calculated to compare their predictive accuracy.

Results: The incidence of AKI on the second day after admission was 10.4% among patients with TBI. Lasso regression identified five potent predictive factors for AKI: glucose, serum creatinine, cystatin C, serum uric acid, and fresh frozen plasma transfusions. The CART analysis showed that glucose, serum uric acid, and cystatin C ranked among the top three in terms of the feature importance of the decision tree model. The AUC value of the decision-tree predictive model was 0.892, which was higher than the 0.854 of the LASSO regression model, although the difference was not statistically significant.

Conclusion: The decision tree model is valuable for predicting AKI among patients with TBI. This tree-based flowchart is convenient for physicians to identify patients with TBI who are at high risk of AKI and prompts them to develop suitable therapeutic strategies.

Keywords: acute kidney injury, decision tree, traumatic brain injury, prediction, machine learning

Introduction

Acute kidney injury (AKI) is a widespread complication that occurs in 7.6–24% of hospitalized patients with traumatic brain injury (TBI).[1–5] AKI can increase the risk of mortality and prolong the length of hospital stay among patients with TBI][1,5–7] The high prevalence of AKI in TBI may be caused by pathophysiological processes after the initial brain injury, including systemic inflammation, excessive sympathetic activation, hypoperfusion, and the common use of nephrotoxic medications such as hypertonic saline, blood product transfusion, and nephrotoxic antibiotics.[8–10] The lack of drugs to alleviate and prevent renal injury emphasizes the importance of identifying patients with TBI who are at a high risk of AKI in the early stages. For TBI patients with a high likelihood of developing renal dysfunction, physicians should cautiously use or even withdraw nephrotoxic drugs and operations and try to maintain stable hemodynamics.

Several studies have identified various risk factors for AKI and developed predictive models for AKI in patients with TBI using conventional logistic or Cox regression.[3,11–13] Compared to this conventional statistical method, machine learning has attracted much attention from researchers because of its advantages, such as handling complex datasets effectively and

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performing well in analyzing nonlinear data.[14] Many studies have used various machine learning algorithms to predict outcomes, including the mortality and functional status of patients with TBI.[15–19] However, few studies have explored the value of machine learning algorithms in predicting perioperative complications, especially AKI, in patients with TBI. As a classic machine learning algorithm, the decision tree algorithm has several advantages, including a fast calculation speed, convenient visualization, and applicability for high-dimensional data. It has been widely used to evaluate the prognosis and complications of other diseases such as pneumonia, cancer, stroke.[20–23] Therefore, we designed this study to construct a predictive model for AKI in patients with TBI using the decision tree method and compared its predictive accuracy with that of a conventional logistic regression-based predictive model.

Materials and Methods

Patients

Patients admitted to the emergency department of West China Hospital for TBI between January 2015 and June 2019 were eligible for this study. However, patients were excluded if they met the following criteria: (1) transferred from other hospitals after brain injury, (2) admitted to our hospital 6 h after brain injury, (3) lack of records of included variables, and (4) AKI occurred during the first day after admission. Finally, 376 patients were included in this study. This study was approved by the ethics committee of West China Hospital and conducted in accordance with the Declaration of Helsinki. Informed consent forms for joining the observational study were regularly signed by the patients themselves or their legally authorized representatives once the patients were admitted to our hospital.

Data Collection

Demographic information, injury mechanisms, and vital signs on admission, including systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate, were recorded. Trauma scores including GCS; Abbreviated Injury Score (AIS) of the head, chest, abdomen, and limbs; and Injury Severity Score (ISS) were collected to reflect the injury severity of the brain and other body regions. Laboratory tests included white blood cells, neutrophils, lymphocytes, monocytes, platelets, hemoglobin, albumin, prothrombin time, red cell distribution width, glucose, lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen, serum creatinine, serum uric acid, serum cystatin C, chloride, potassium, phosphorus, total cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein. Laboratory tests were performed by analyzing the first blood sample collected on admission. Radiological signs, including epidural hematoma, subdural hematoma, subarachnoid hemorrhage, intraventricular hemorrhage, and diffuse axonal injury, and surgical options, including decompressive craniectomy and hematoma evacuation, were selected as variables. Additionally, medications during the first 24 h after admission, including platelet transfusion, fresh frozen plasma transfusion, cryoprecipitation transfusion, and furosemide use, were collected. The outcome of this study was the occurrence of AKI since the second day after admission. AKI was confirmed using the Kidney Disease Improving KDIGO serum creatinine criteria.

Statistical Analysis

Categorical and continuous variables were presented as numbers (percentage) and mean ± standard deviation (normal distribution) or median (interquartile range) (non-normal distribution), respectively. The normality of the variables was verified using the Kolmogorov–Smirnov test. Differences in continuous variables between the two groups were compared using the Independent Student's *t*-test (normal distribution) and the Mann–Whitney *U*-test (non-normal distribution). The χ^2 test or Fisher's exact test was used to compare the differences in categorical variables.

Minimizing the collinearity of the included variables and avoiding overfitting of these variables, least absolute shrinkage and selection operator (LASSO) regression was used to identify predictors of AKI with nonzero coefficients. Identifying the strongest predictors from a number of variables for outcomes with a small sample size is an advantage of LASSO regression, which fits the characteristics of our dataset, with 39 AKI occurrences and 49 independent variables. Predictors with non-zero coefficients were then combined to construct a predictive model for AKI in patients with TBI using multivariate logistic regression.

A decision tree predictive model for AKI in TBI was constructed using the classification and regression tree (CART) algorithm. The decision tree was set with a maximum depth of 10 layers, minimum of 40 cases for each parent node, and minimum of 20 cases for each child node. Branches were optimally split based on the Gini impurity index and pre-pruning was performed to avoid overfitting the CART model. A 10-fold cross-validation method was used to internally validate the CART model. This method randomly divides the original dataset into ten subsets of equal sizes, with nine subsets as the training set and the other as the validation set. This procedure was repeated 10 times, with each of the 10 subsets used once as the validation set. The optimal CART model was selected on the basis of its predictive accuracy.

Receiver operating characteristic (ROC) curves of the LASSO regression predictive model and the CART model were drawn, and the area under the ROC curves (AUC) was calculated to compare their predictive accuracy (the Z test was used to compare the AUC).

Statistical p value was defined as a two-sided p-value of < 0.05. SPSS software (version 22.0; IBM Corp., Armonk, NY, USA) and R software (version 3.6.1; R Foundation) (packages including glmnet, caret, rms, rpart, and rpart.plot) were used for all statistical analyses and figure drawings.

Results

Baseline Characteristics of Included TBI Patients

A total of 376 patients had an AKI incidence of 10.4% (Table 1). The AKI group was older ($p = 0.013$) and had a lower GCS score ($p < 0.001$) than the non-AKI group. The AIS head ($p = 0.001$), AIS thoracic ($p = 0.026$), and ISS ($p = 0.002$) scores were higher in the AKI group. Laboratory tests showed that the AKI group had lower levels of lymphocytes ($p = 0.001$), hemoglobin ($p = 0.012$), albumin ($p = 0.003$), and total cholesterol ($p = 0.005$), and higher levels of prothrombin time ($p = 0.003$), red cell distribution width ($p = 0.002$), glucose ($p <0.001$), blood urea nitrogen ($p = 0.005$), serum creatinine ($p <0.001$), serum uric acid ($p <0.001$), cystatin C ($p <0.001$), and chloride ($p <0.001$). Records of medical drugs showed that transfusion rates of platelets ($p = 0.002$) and fresh frozen plasma ($p <0.001$) were higher in the AKI group. The length of ICU stay ($p = 0.533$) did not differ between the AKI and non-AKI groups, whereas the total length

Table 1 Baseline Characteristics of TBI Patients Grouped by AKI

Variables	Overall Patients (n=376)	Patients Without AKI (n=337, 89.6%)	Patients with AKI (n=39, 10.4%)	p
Age (years)	42 (25.00–56)	41 (24–54)	47 (38–64)	0.013
Sex (male)	285 (75.8%)	253 (75.1%)	32 (82.1%)	0.444
Injury mechanism				0.108
Traffic accident	228 (60.6%)	206 (61.1%)	22 (56.4%)	
High falling	76 (20.2%)	67 (19.9%)	9 (23.1%)	
Stumble	45 (12.0%)	37 (11.0%)	8 (20.5%)	
Others	27 (7.2%)	27 (8.0%)	0	
Vital signs on admission				
Systolic blood pressure (mmHg)	122 (106–138)	121 (106–138)	123 (105–148)	0.600
Diastolic blood pressure (mmHg)	73±16.26	73±15.49	73±22.08)	0.952
Heart rate (min^{-1})	98 (80–116)	98 (80–118)	97 (82–108)	0.354
Body temperature (°C)	36.7 (36.5–37.0)	36.7 (36.5–37.0)	36.8 (36.5–37.0)	0.676
Respiratory rate (min^{-1})	20 (16–22)	20 (16–22)	20 (17–24)	0.335

(*Continued*)

Table 1 (Continued).

Variables	Overall Patients (n=376)	Patients Without AKI (n=337, 89.6%)	Patients with AKI (n=39, 10.4%)	p
Anisocoria	109 (29.0%)	96 (28.5%)	13 (33.3%)	0.656
GCS	6 (5–9)	6 (5–10)	5 (3–6)	<0.001
AIS head	4 (3–5)	4 (3–5)	5 (4–5)	0.001
AIS thoracic	0	0	0 (0–2)	0.026
AIS abdomen	0	0	0	0.995
AIS limbs	0	0	0	0.742
Injury severity score	25 (16–25)	22 (14–25)	25 (16–31)	0.002
Laboratory test				
White blood cell (10^9/L)	14.80 (10.77–18.97)	14.48 (10.51–18.89)	15.65 (12.93–20.37)	0.107
Neutrophil (10^9/L)	11.59 (8.05–15.15)	11.39 (7.97–15.15)	12.32 (8.85–15.31)	0.326
Lymphocyte (10^9/L)	0.85 (0.56–1.23)	0.88 (0.57–1.32)	0.64 (0.38–0.89)	0.001
Monocyte (10^9/L)	0.64 (0.44–0.88)	0.65 (0.44–0.87)	0.58 (0.45–1.06)	0.900
Platelet (10^9/L)	128 (80–185)	129 (81–193)	105 (68–164)	0.067
Hemoglobin (g/L)	91 (77–111)	93 (78–111)	82 (74–90)	0.012
Albumin (g/L)	31.81±7.93	32.22±7.92	28.23±7.17	0.003
Prothrombin time (s)	13.5 (12.1–15.3)	13.3 (12.1–15.0)	14.7 (12.2–18.6)	0.033
Red cell distribution width (%)	14.2 (13.3–15.0)	14.1 (13.2–14.9)	14.8 (14.1–16.0)	0.002
Glucose (mmol/L)	9.50 (6.96–12.99)	9.11 (6.68–12.53)	14.52 (9.76–17.81)	<0.001
Lactate dehydrogenase (U/L)	362 (275–493)	357 (271–491)	387 (293–555)	0.289
Alkaline phosphatase (U/L)	69 (49–98)	69 (50–99)	58 (47–86)	0.194
Blood urea nitrogen (mmol/L)	5.91 (4.64–7.80)	5.88 (4.57–7.65)	7.22 (5.40–9.37)	0.005
Serum creatinine (umol/L)	68 (51–85)	65 (49–83)	88 (71–117)	<0.001
Serum uric acid (umol/L)	265 (179–372)	251 (169–354)	383 (333–505)	<0.001
Serum cystatin C (mg/L)	0.77 (0.63–0.93)	0.76 (0.63–0.91)	0.92 (0.74–1.25)	<0.001
Chloride (mmol/L)	110.6 (105.6–117.1)	110.0 (105.1–116.6)	115.8 (111.1–128.3)	<0.001
Potassium (mmol/L)	3.72 (3.33–4.11)	3.72 (3.34–4.11)	3.70 (3.27–4.06)	0.650
Phosphorus (mmol/L)	0.84 (0.58–1.13)	0.84 (0.60–1.16)	0.85 (0.54–1.08)	0.625
Total cholesterol (g/L)	2.80 (2.06–3.66)	2.87 (2.15–3.67)	2.28 (1.61–2.95)	0.005
Triglyceride (g/L)	1.07 (0.68–1.60)	1.07 (0.69–1.59)	0.97 (0.66–1.70)	0.634
High density lipoprotein (g/L)	1.00 (0.70–1.31)	1.01 (0.69–1.33)	0.90 (0.74–1.26)	0.833
Low density lipoprotein (g/L)	1.62 (1.04–2.22)	1.65 (1.04–2.23)	1.45 (0.94–2.06)	0.402

(*Continued*)

Table 1 (Continued).

Variables	Overall Patients (n=376)	Patients Without AKI (n=337, 89.6%)	Patients with AKI (n=39, 10.4%)	p
Radiological findings				
Epidural hematoma	42 (11.2%)	38 (11.3%)	4 (10.3%)	1.000
Subdural hematoma	89 (23.7%)	78 (23.1%)	11 (28.2%)	0.614
Subarachnoid hemorrhage	208 (55.3%)	184 (54.6%)	24 (61.5%)	0.512
Intraventricular hemorrhage	20 (5.3%)	18 (5.3%)	2 (5.1%)	1.000
Diffused axonal injury	87 (23.1%)	76 (22.6%)	11 (28.2%)	0.554
Treatments				
Hematoma evacuation	129 (34.3%)	114 (33.8%)	15 (38.5%)	0.690
Length of ICU stay (days)	4 (1–18)	4 (1–18)	3 (2–13)	0.533
Length of hospital stay (days)	13 (5–28)	14 (5–31)	7 (3–16)	0.006
In-hospital mortality	168 (44.7%)	136 (40.4%)	32 (82.1%)	<0.001

Abbreviations: GCS, Glasgow Coma Scale; AIS, Abbreviated Injury Score.

of hospital stay was shorter in the AKI group ($p = 0.006$). The overall patients mortality was 44.7%. The AKI group had a significantly higher in-hospital mortality rate than the non-AKI group ($p < 0.001$).

Value of CART and Lasso Regression Models for Predicting AKI in TBI Patients

Lasso regression revealed five potent predictive factors for AKI: glucose, serum creatinine, cystatin C, serum uric acid, and fresh frozen plasma transfusions (Figure 1A and B). A logistic regression-based predictive model was constructed using these five factors. A decision tree model for predicting AKI was constructed using CART analysis, as shown in Figure 2. At the first node from the root, The SUA <314 was the most significant categorical discriminator to identify AKI risk in TBI patients. Cystatin C <1.00 and glucose <15.00 were at the second node. 40% of TBI patients who were SUA <314 and glucose <15.00, had an AKI risk of 22.0%. The feature importance of each variable analyzed using CART is shown in Figure 3. The AUC values of the decision tree and logistic regression models were 0.892 and 0.854, respectively (Table 2) (Figure 4). The AUC value of the decision tree model was higher than that of the logistic regression model, although the difference was not statistically significant ($Z = 1.0209$, $p > 0.05$). The decision tree model had a higher specificity (0.821), whereas the logistic regression model had a higher sensitivity (1.000) for predicting AKI in patients with TBI.

Discussion

The AKI incidence in TBI patients included in this study was 10.4%, which was similar to the 7.6% to 24% reported in previous studies.[1–5] The relatively low incidence of AKI in this study is attributable to the exclusion of patients who developed AKI on the first day after admission. These patients usually show a rapid increase in serum creatinine level after admission and were therefore excluded due to obvious signs of renal dysfunction without the need for prediction, and immediate AKI after admission was difficult to avoid in the short-term. The CART algorithm in our study discovered four variables to split the three branches: glucose, serum uric acid, serum cystatin, and serum chloride levels.

Glucose level was used to split branches with higher glucose levels, indicating a higher likelihood of AKI in our constructed decision tree. Many previous studies have confirmed that hyperglycemia is a risk factor for AKI in various patients, such as those with acute coronary syndrome, myocardial infarction, and sepsis.[24–28] Stress-induced hyperglycemia is prevalent in patients with TBI, with reported incidences ranging from 7.8% to 29.4%.[29–33] Acute hyperglycemia

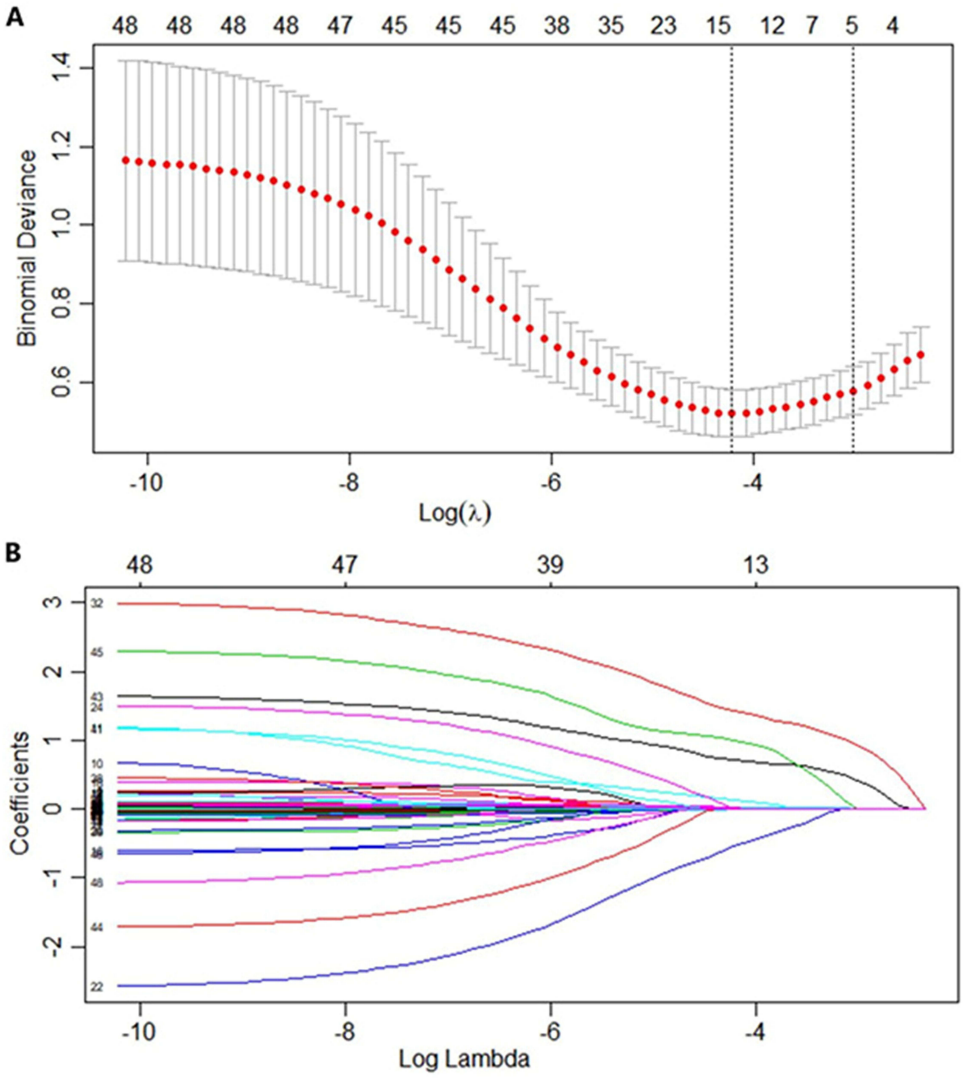

Figure 1 (**A**) The predictive factors selection using LASSO binary logistic regression. Two dotted vertical lines mark the optimal values by minimum criteria and 1-s.e. criteria. Five variables were selected by LASSO binary logistic regression including glucose, serum creatinine, cystatin C, serum uric acid and fresh frozen plasma transfusion. (**B**) LASSO coefficient profiles of 49 variables.
Abbreviation: LASSO, least absolute shrinkage and selection operator.

after trauma causes loss of the glycocalyx layer, endothelial cell inflammation, and coagulation activation, which may also aggravate renal injury.[34]

Two other indices indicating renal dysfunction, serum uric acid and serum cystatin C levels, were also incorporated into the decision tree. As the end product of purine metabolism in the body, uric acid is mainly excreted from the kidneys. Renal dysfunction with a reduced glomerular filtration rate (GFR) may lead to uric acid accumulation and increased blood concentration. Cystatin C is also filtered through the glomerulus and completely reabsorbed by the proximal renal tubule. Increased serum cystatin C level may indicate impaired renal function. Previous studies have verified the predictive value of serum uric acid and cystatin C in patients with AKI, such as those with cirrhosis, myocardial infarction, and those treated with cardiac surgery or cystectomy.[35–43]

Finally, serum chloride level was included in the constructed decision tree to split the parent node. As shown in Figure 2, patients with chloride ≥115.0 mmol/L had a higher incidence of AKI than those with chloride <115.0 mmol/L. Hyperchloremia has been confirmed to be independently associated with AKI in some patients, including subarachnoid hemorrhage, sepsis, intracerebral hemorrhage, and brain tumor resection.[44–49] Furthermore, one study found that

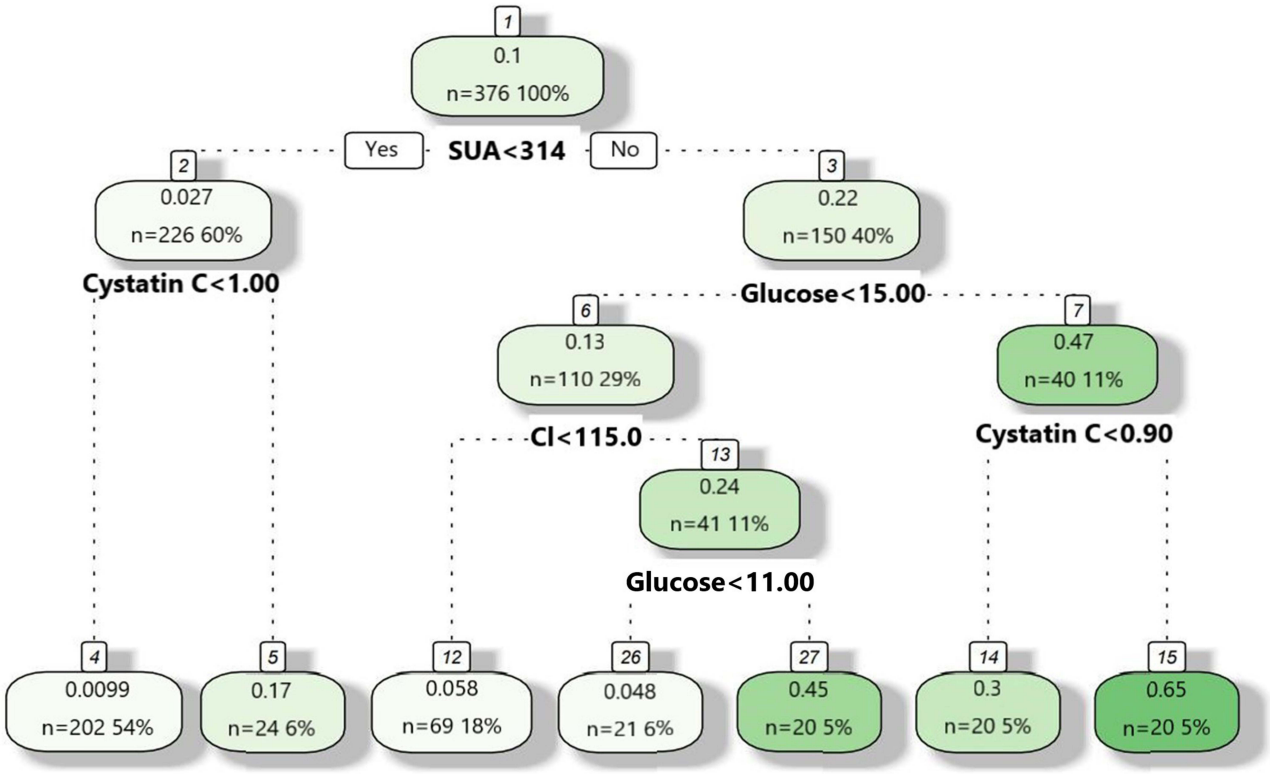

Figure 2 Decision tree model for the prediction of AKI in included TBI patients using CART analysis.
Abbreviations: Cl, serum chloride; SUA, serum uric acid; AKI, acute kidney injury; TBI, traumatic brain injury; CART, Classification And Regression Tree.

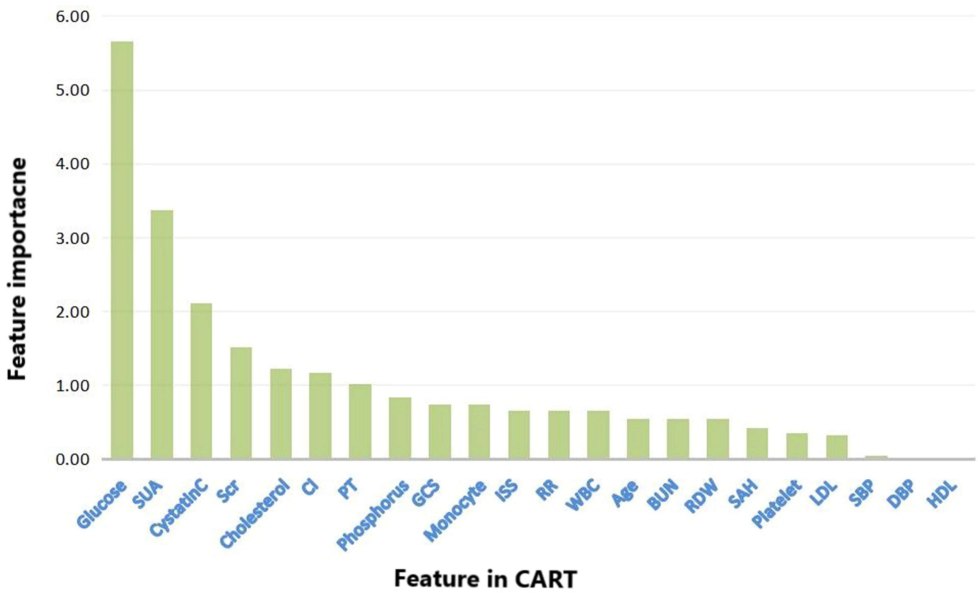

Figure 3 Feature importance of variables recognized by CART analysis.
Abbreviations: CART, Classification And Regression Tree; SUA, serum uric acid; Scr, serum creatinine; Cl, serum chloride; PT, prothrombin time; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; RR, respiratory rate; WBC, white blood cell; BUN, blood urea nitrogen; RDW, red cell distribution width; SAH, subarachnoid hemorrhage; LDL, low density cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density cholesterol.

Table 2 Comparison of Predictive Accuracy Between CART Model and Lasso Based Predictive Model

	AUC	95% CI	Sensitivity	Specificity
CART	0.892	0.838–0.947	0.846	0.821
Lasso regression	0.854	0.806–0.903	1.000	0.620

Abbreviations: CART, Classification and Regression Tree; AUC, area under the receiver operating characteristic curve; CI, confidence interval.

prolonged hyperchloremia duration, but not hyperchloremia occurrence, was independently correlated with AKI in patients.[13] A potential mechanism underlying this association has been proposed in previous studies, which revealed that excessive chloride can induce renal vasoconstriction and reduce renal cortical perfusion.[50,51]

Many studies have explored the value of machine learning algorithms in predicting outcomes in patients.[15–17,19,52,53] However, few studies have explored the effectiveness of machine-learning algorithms in predicting subsequent complications in hospitalized patients with TBI. TBI is a complex disease that involves pathophysiological processes in systemic organs. Non-neurological complications are prevalent in patients with TBI and are associated with poor outcomes. Evaluating the risk of complications after admission may be helpful for physicians and surgeons to develop personalized medical strategies to improve the prognosis of patients with TBI.

In this study, we developed a decision tree to evaluate the risk of AKI in hospitalized TBI patients using the CART algorithm. Decision trees are popular in medical decision-making because of their advantages, including fast calculation speed, high accuracy, collective processing of continuous and categorical variables, applicability to high-dimensional data unaffected by data scaling, and convenient visualization as a form of flowchart. The CART is a learning method that outputs the conditional probability distribution of the random variable Y under the given input random variable X conditions. The advantages of CART include strong interpretability, good stability, excellent visualization effect, high computational efficiency. The CART can present results in an intuitive and easily understandable way, with each node representing a feature and

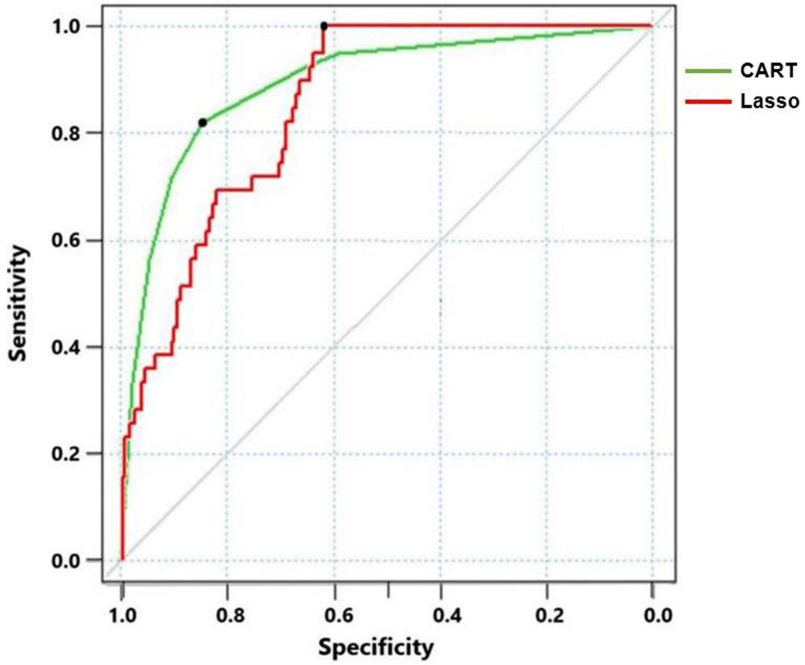

Figure 4 Receiver operating characteristic curve of CART and the LASSO logistic regression models for predicting AKI in included TBI patients. The AUC of decision tree model and Lasso regression model were 0.892 (0.838–0.947) and 0.854 (0.806–0.903), respectively.
Abbreviations: AUC, area under the receiver operating characteristic curve; CART, Classification And Regression Tree; LASSO, least absolute shrinkage and selection operator; AKI, acute kidney injury; TBI, traumatic brain injury.

each branch representing a decision, thus clearly explaining the relationships between data and the decision-making process in a graphical way. Also, the CART has relatively low computational complexity and can train models in a short period of time. The CART has wide applications in sociology, economics, and medicine. In medicine, CART can be used to diagnose diseases, predict disease progression and prognosis, and develop treatment plans. One study developed a CART model to assist clinical prediction for tracheostomy in patients with traumatic cervical spinal cord injury using three simple indexes including American Spinal Injury Association classification, neurological level of impairment, Injury Severity Score.[54] Another study constructed a classification and regression tree which could identify subgroups of childhood type 1 diabetes using three parameters including age, hemoglobin A1c and body mass index.[55]

The predictive value of the decision-tree model in our study was not inferior to that of the Lasso regression based predictive model. The difference in AUC between these two models may be statistically significant in future validation cohorts with larger sample sizes. Regardless, compared with the LASSO regression model requiring a particular calculation of AKI probability, the decision tree model is more comprehensive and easier to evaluate the risk of AKI. This could prompt physicians to reduce the use of nephrotoxic medications to prevent the occurrence or progression of AKI in clinical practice.

This study had several limitations. First, the decision tree model was developed using patients from a single medical center and internally validated using 10-fold cross validation. Selection bias is inevitable, and the stability and generalizability of this model should be externally verified in other medical centers with larger sample sizes. Second, although many factors were selected for this study, there are still some potential factors, such as nephrotoxic antibiotics, that have not been included in the analysis. Third, the dynamic fluctuation of filtration markers, including cystatin C and serum uric acid, was not recorded, so we could not analyze the value of this fluctuation, which may better reflect deteriorating renal function.

Conclusion

The decision tree predictive model, composed of glucose, cystatin C, serum uric acid, and chloride, is valuable for predicting AKI among patients with TBI. This tree-based flowchart is visual and convenient for physicians to identify patients with TBI with a high risk of AKI and consequently prompts physicians to develop suitable therapeutic strategies.

Data Sharing Statement

The datasets are available from the corresponding author upon reasonable request.

Ethical Approval and Informed Consent

This study was approved by the ethics committee of West China Hospital and conducted in accordance with the Declaration of Helsinki. Informed consent forms for joining the observational study were regularly signed by the patients themselves or their legally authorized representatives once the patients were admitted to our hospital.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Ruoran Wang and Jing Zhang are co-first authors for this study. The authors declare that they have no conflicts of interest for this work.

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