Serum antithrombin III level predicts acute kidney injury in patients with traumatic brain injury

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Abstract. As an important anticoagulant molecule, antithrombin III (ATIII) has been confirmed to inhibit inflammation and to alleviate renal ischemia-reperfusion injury. The present study aimed to explore the relationship between serum ATIII level and acute kidney injury (AKI) in patients with traumatic brain injury (TBI). The clinical data of patients diagnosed with TBI and hospitalized in the West China Hospital (Chengdu, China) between January 2015 and June 2019 were collected. Logistic regression analysis was performed to analyze the relationship between ATIII and AKI and to construct predictive models. The area under the receiver operating characteristic curve (AUC) was calculated to evaluate the predictive value of ATIII and models were constructed. As a result, 203 patients with TBI were included in the present study. A total of 43 (19.7%) patients developed AKI at 24 h after admission. Compared with the non-AKI group, the AKI group had a lower Glasgow Coma Scale, injury severity score and ATIII, but had a higher glucose level, prothrombin time, levels of blood urea nitrogen and serum creatinine (SCr) and higher transfusion rate of fresh frozen plasma (FFP), red blood cell and hydroxyethyl starch. The mortality of the AKI group was 65.1%, which was higher compared with the 30.0% of the non-AKI group. SCr, ATIII and transfusion of FFP were independently associated with development of AKI after TBI. The AUC of the constructed three-factors predictive model was 0.850, which was higher compared with the AUC of 0.759 of only ATIII. Overall, ATIII was an effective predictive marker of AKI after TBI. Evaluating serum ATIII level and maintaining normal ATIII level may be beneficial for physicians to reduce the occurrence of AKI in patients with TBI.

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Key words: antithrombin III, acute kidney injury, traumatic brain injury, predictive model

Introduction

Traumatic brain injury (TBI) remains a serious public health concern that ranks first among causes of trauma-associated mortality and disability (1). It is estimated that ~69 million individuals suffer TBI each year worldwide (2). The unfavorable mortality, disability and the widespread prevalence of TBI brings a heavy economic burden to society and to patients families (1). The severity of intracranial injury and neurological complications increase the risk of an unfavorable outcome after TBI. While non-neurological complications also commonly occur after TBI and have been confirmed to be associated with the adverse outcome of patients with TBI (3-5). Occurring in 7.6-23% of patients with TBI, acute kidney injury (AKI) is a common type of non-neurological organ dysfunction, which has been verified to be correlated with increased mortality in patients with TBI (6-11). Therefore, evaluating renal function, predicting the possible occurrence of AKI and sequentially adjusting treatment strategies in early stage after initial brain injury is beneficial for physicians to reduce the risk of AKI development and improve prognosis of patients with TBI.

Encoded by SerpinC1, antithrombin III (ATIII) is a serine protease inhibitor that plays an anticoagulant role in the coagulation cascade (12). In addition to the pivotal role involved in anticoagulation, ATIII has been revealed to have anti-inflammation properties in previous studies (13-16). Previously, several studies explored the beneficial effects of ATIII on renal protection and found that renal ischemia-reperfusion injury in a rat model can be alleviated by ATIII through coagulation-independent anti-inflammation effects (17-19). In addition, the association between decreased ATIII level and the occurrence of AKI has been confirmed in several clinical settings including acute severe pancreatitis, sepsis and in patients undergoing cardiac surgery (17,20,21). However, to the best of our knowledge, the relationship between ATIII level and the development of AKI in patients with TBI has not been explored. Thus, the present study aimed to test the hypothesis that ATIII level is associated with the occurrence of AKI after TBI.

Materials and methods

Study population. The present retrospective observational study was performed in West China Hospital (Chengdu, China). Patients admitted to West China Hospital for TBI and who then received treatments in the neuro intensive care unit (NICU) between January 2015 and June 2019 were eligible for the present study. Patients with low consciousness, unstable hemodynamics and intracranial hypertension who required intensive monitoring and organ function support were transferred from the emergency department to the NICU within 24 h after admission. Therefore, the included patients were mainly diagnosed with moderate to severe TBI. The present study confirmed the diagnoses of TBI according to radiological signs of computed tomography (CT) during hospitalization. There were four exclusion criteria: i) Transferred from other hospitals after initial injury; ii) hospitalized in West China Hospital for <24 h; iii) history of surgery or severe infection within 4 weeks before TBI; and iv) lack of complete relevant data. The screening diagram was shown as seen in Fig. 1. After screening, 203 patients with the median age of 44 and male ratio of 80.3% were finally included in the present study. This study was approved by the ethics committee of West China Hospital and conducted according to the Declaration of Helsinki. Informed consent form of each patient was routinely signed by themselves or their authorized legal representatives.

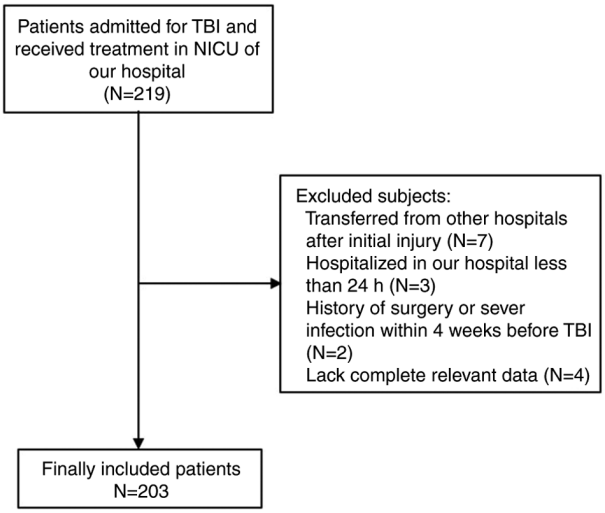

Figure 1. Flowchart diagram of TBI patients inclusion. TBI, traumatic brain injury.

Data collection. All clinical and laboratory variables were retrospectively reviewed from the records of the electronic medical record system. The present study included demographic characteristics such as age and sex, injury mechanisms and vital signs on admission including systolic blood pressure, diastolic blood pressure, heart rate, body temperature and respiratory rate. Occurrence of anisocoria, injury severity score (ISS) and Glasgow Coma Scale (GCS) on admission were also recorded (22). Variables of laboratory test including serum ATIII level were obtained by analyzing the first blood samples collected when patients were admitted to the emergency department of West China Hospital. Acute liver injury was confirmed based on the liver function score of sequential organ failure assessment score, namely total bilirubin ≥20.5 μmol/l (23). Marshall CT score and specified injury types, including subarachnoid hemorrhage and intraventricular hemorrhage, were collected based on the findings of the CT scans (24). AKI was diagnosed according to the KDIGO criteria (25). As the aim of the present study was to predict the development of AKI during hospitalizations, any AKIs that occurred on the first day after admission were excluded and only AKIs that occurred after the second day after admission were selected as primary outcome (since the treatment of first day is mainly focused on emergency treatment and maintaining vital signs). In addition, AKI on the first day is difficult to identify because the AKI is diagnosed based on fluctuation of SCr and the level of SCr may not be measured more than one time within the first day after admission. Records of blood product transfusion, drugs reducing intracranial pressure, nephrotoxic antibiotics and surgery types were included in the present study. The indications for fresh frozen plasma (FFP) in West China Hospital for trauma patients were shown as follows: i) Acute massive hemorrhage (blood loss ≥70 ml/kg within 24 h); and ii) prothrombin time (PT) or activated partial thromboplastin time (APTT) prolongation >1.5 times. Records of aforementioned medicine and operation for AKI group were collected until AKI developed while those for non-AKI group were collected during the whole hospitalization.

Statistical analysis. The Kolmogorov-Smirnov test was used to verify the normality of the included variables. Normally distributed variables were presented as mean ± standard deviation while non-normally distributed variables were presented as median (interquartile range). And categorical variables were presented as counts (percentage). The present study conducted unpaired Student's t-test to analyze the difference between two groups of normally distributed variables. And the difference between two groups of non-normally distributed variables were testified by utilizing Mann-Whitney U test. χ^2 test or Fisher's exact test were performed to verify the difference between two groups of categorical variables. To discover potential risk factors for AKI in included patients with TBI, univariate logistic regression analysis was first conducted to present the relationship without adjusting confounding effects. Odds ratio (OR) and 95% confidence intervals (CI) of each risk factors were calculated and shown. Because of the numerous included variables and limited number of outcomes, the least absolute shrinkage and selection operator (LASSO) regression, which could minimize the collinearity of selected risk factors and avoid overfitting of these factors, was performed to identify predictors with non-zero coefficients. Identifying the strongest predictors from plenty of potential risk factors for targeted outcome with relatively small quantity is the advantage of LASSO regression. Predictors with non-zero coefficients were included in multivariate logistic regression analysis to construct models for predicting AKI in included patients with TBI. Finally, receiver operating characteristic (ROC) curve was drawn and area under the ROC curve (AUC) value was calculated to evaluate the predictive value of single ATIII, SCr and constructed models. The corresponding sensitivity and specificity of ATIII and constructed model were shown. Z test was conducted to verify the difference

Table I. Baseline characteristics of non-AKI group and AKI group in included patients with TBI.

Variables	Overall patients (n=203)	Non-AKI group (n=160; 80.3%)	AKI group (n=43; 19.7%)	P-value
Age, years	44 (28-58)	43 (27-55)	47 (33-64)	0.057
Male sex, n (%)	163 (80.3%)	126 (78.8%)	37 (86.0%)	0.270
Injury mechanism				0.152
Traffic accident	122 (60.1%)	100 (62.5%)	22 (51.2%)	
High fall	47 (23.2%)	34 (21.3%)	13 (30.2%)	
Stumble	21 (10.3%)	14 (8.8%)	7 (16.3%)	
Others	13 (6.4%)	12 (7.5%)	1 (2.3%)	
Vital signs on admission				
Systolic blood pressure, mmHg	123 (108-138)	123 (110-138)	117 (101-145)	0.324
Diastolic blood pressure, mmHg	73.5±16.3	74.2±14.5	71.1±21.6	0.384
Heart rate, min^{-1}	98 (80-120)	98 (80-120)	100 (80-125)	0.901
Body temperature,˚C	36.8 (36.5-37.2)	36.8 (36.5-37.3)	36.8 (36.5-37.0)	0.520
Respiratory rate, min^{-1}	20 (17-24)	20 (17-24)	20 (17-22)	0.588
Anisocoria	76 (37.4%)	60 (37.5%)	16 (37.2%)	0.972
GCS	6 (5-7)	6 (5-8)	5 (3-7)	0.002
ISS	25 (16-25)	24 (16-25)	25 (16-29)	0.009
Laboratory tests				
Glucose, mmol/l	9.70 (7.23-13.31)	8.94 (6.77-12.61)	12.68 (8.83-15.45)	<0.001
White blood cell, 10^9/l	15.45 (11.27-20.43)	15.38 (11.33-20.39)	15.65 (10.05-20.73)	0.974
Neutrophil, 10^9/l	11.75 (8.70-15.81)	11.81 (9.00-15.76)	11.63 (7.34-16.9)	0.713
Lymphocyte, 10^9/l	0.80 (0.53-1.12)	0.79 (0.53-1.18)	0.80 (0.50-1.05)	0.358
Platelet, 10^9/l	113 (80-169)	122 (86-178)	100 (58-161)	0.031
Albumin, g/l	31.47±5.63	32.15±5.22	28.95±6.39	0.001
Hemoglobin, g/l	88 (77-106)	92 (79-109)	79 (72-88)	<0.001
Fibrinogen, mg/l	2.53 (1.63-4.07)	2.81 (1.71-4.49)	1.94 (1.15-3.31)	0.006
D-dimmer, mg/l	15.24 (7.37-34.99)	14.76 (6.10-33.96)	17.27 (10.38-38.00)	0.124
Prothrombin time, sec	13.6 (12.2-15.4)	13.4 (12.0-15.0)	14.6 (13.3-18.2)	0.002
APTT, sec	27.4 (26.6-28.9)	27.2 (26.5-27.9)	31.3 (28.8-33.2)	
ATIII, %	77.0±19.9	81.0±18.4	62.1±18.3	<0.001
Blood urea nitrogen, mmol/l	5.93 (4.70-8.51)	5.75 (4.46-7.82)	7.70 (5.41-11.44)	0.001
Serum creatinine, μmol/l	71 (55-98)	68 (52-86)	98 (76-131)	<0.001
Acute liver dysfunction	58 (28.6%)	47 (29.4%)	11 (25.6%)	0.622
Radiological findings				
Marshall CT score	4 (3-6)	4 (3-6)	6 (3-6)	0.280
Subarachnoid hemorrhage, n (%)	87 (42.9%)	68 (42.5%)	19 (44.2%)	0.843
Intraventricular hemorrhage, n (%)	8 (3.9%)	8 (5.0%)	0	0.207
Blood product transfusion, n (%)				
Fresh frozen plasma	52 (25.6%)	28 (17.5%)	24 (55.8%)	<0.001
Fibrinogen transfusion	26 (12.8%)	18 (11.3%)	8 (18.6%)	0.218
Hydroxyethyl starch	68 (33.5%)	48 (30.0%)	20 (46.5%)	0.045
Red blood cell transfusion	76 (37.4%)	52 (32.5%)	24 (55.8%)	0.006
Drugs reducing ICP, n (%)				
Mannitol	158 (77.8%)	124 (77.5%)	34 (79.1%)	0.825
Fructose glycerol	21 (10.3%)	15 (9.4%)	6 (14.0%)	0.401
Hypertonic saline	78 (38.4%)	70 (43.8%)	8 (18.6%)	0.002
Furosemide	70 (34.5%)	53 (33.1%)	17 (39.5%)	0.436
Nephrotoxic antibiotics, n (%)				
Vancomycin	50 (24.6%)	45 (28.1%)	5 (11.6%)	0.018
Meropenem	27 (13.3%)	22 (13.8%)	5 (11.6%)	0.712

Table I. Continued.

Variables	Overall patients (n=203)	Non-AKI group (n=160; 80.3%)	AKI group (n=43; 19.7%)	P-value
Surgical operations				
Decompressive craniectomy, n (%)	74 (36.5%)	53 (33.1%)	21 (48.8%)	0.061
Hematoma evacuation, n (%)	87 (42.9%)	66 (41.3%)	21 (48.8%)	0.374
Length of ICU stay, days	15 (5-27)	16 (6-27)	11 (2-27)	0.177
Length of hospital stay, days	24 (10-41)	26 (13-42)	13 (3-35)	0.001
In-hospital mortality, n (%)	76 (37.4%)	48 (30.0%)	28 (65.1%)	<0.001

Normally and non-normally distributed variables are presented as mean ± standard deviation and median (interquartile range), respectively. Categorical variables are presented as counts (percentage). GCS, Glasgow Coma Scale; ISS, injury severity score; APTT, activated partial thromboplastin time; ATIII, antithrombin III; ICP, intracranial pressure; AKI, acute kidney injury; TBI, traumatic brain injury.

of AUC value between single ATIII and constructed models. Two-tailed P<0.05 was considered to indicate a statistically significant difference. SPSS 22.0 Windows software (IBM Corp.) and R (version 3.6.1; R Foundation) were used to carry out all statistical analyses.

Results

Baseline characteristics of included patients with TBI. A total of 203 patients with TBI were finally included in the present study, with 43 developing AKI 24 h after admission (Table I). Among 43 confirmed patients with AKI, 30 patients were confirmed as stage 1, 7 patients confirmed as stage 2 and 6 patients confirmed as stage 3 according to KDIGO criteria. No patient received renal replacement therapy among the included patients with TBI. The age and sex ratio did not differ between the non-AKI group and AKI group (age, 43 vs. 47, P=0.057; sex, 78.8 vs. 86.0%, P=0.270). Among injury mechanisms, traffic accident and high falling ranked the first and the second with rate of 60.1 and 23.2%. Vital signs on admission did not show any significant differences between the non-AKI group and AKI group. The AKI group had significantly lower GCS (5 vs. 6; P=0.002) and higher ISS (25 vs. 24; P=0.009) compared with the non-AKI group. Records of laboratory test presented that AKI group had higher blood glucose (12.68 vs. 8.94; P<0.001), prothrombin time (14.6 vs. 13.4; P=0.002), blood urea nitrogen (BUN; 7.70 vs. 5.75; P=0.001) and SCr (98 vs. 68; P<0.001) compared with the non-AKI group. While the platelet (100 vs. 122; P=0.031), albumin (28.95 vs. 32.15; P=0.001), hemoglobin (79 vs. 92; P<0.001), fibrinogen (1.94 vs. 2.81; P=0.006) and ATIII (62.1 vs. 81.0; P<0.001) levels were significantly lower in the AKI group compared with the non-AKI group. Radiological findings demonstrated that Marshall CT score and incidence of subarachnoid hemorrhage and intraventricular hemorrhage were not significantly different between those two groups. As for blood product transfusion, AKI group were more likely to receive FFP (55.8 vs. 17.5%; P<0.001), hydroxyethyl starch (46.5 vs. 30.0%; P=0.045) and red blood cell (55.8 vs. 32.5%; P=0.006). Considering the drugs reducing intracranial pressure (ICP), hypertonic saline was less likely to be used in the AKI group (18.6 vs. 43.8%; P=0.02). In addition, vancomycin was also less likely to be used in the AKI group (11.6 vs. 28.1%; P=0.018). The AKI group had a significantly higher in-hospital mortality rate compared with the non-AKI group (65.1 vs. 30.0%; P<0.001). Furthermore, the length of ICU stay (11 vs. 16; P=0.177) and length of hospital stay (13 vs. 26; P=0.001) were both shorter in the AKI group due to the notable early mortalities among the AKI group.

Univariate logistic regression analysis of risk factors for AKI in patients with TBI. Univariate logistic regression analysis showed that ISS (P=0.005), glucose (P=0.001), BUN (P=0.035), prothrombin time (P=0.001), SCr (P<0.001) and transfusion of FFP (P<0.001), hydroxyethyl starch (P=0.044) and RBC (P=0.006) were potential risk factors for AKI after TBI (Table II). Whereas GCS (P=0.004), platelet (P=0.035), albumin (P=0.001), hemoglobin (P=0.002), fibrinogen (P=0.007), ATIII (P<0.001) and usage of hypertonic saline (P=0.004) and vancomycin (P=0.032) were negatively associated with occurrence of AKI after TBI.

Value of ATIII and constructed predictive models for predicting AKI after TBI. Utilizing LASSO regression, SCr, ATIII and transfusion of FFP were finally recognized as the most potent predictors of AKI in included patients with TBI (Table III; Fig. 2A and B). To enhance predictive accuracy, multivariate logistic regression was performed to construct predictive models incorporating these three factors. The AUC value of single ATIII and SCr was 0.759 and 0.760, respectively (Table IV; Fig. 3). And the AUC value of three-factors predictive model was 0.850. After removing ATIII, two-factors model composed of SCr and transfusion of FFP had lower AUC, but without statistical significance (0.831 vs. 0.850; Z=0.4404; P>0.05). The two-factors model had a higher AUC compared with single ATIII (0.831 vs. 0.759; Z=1.3582; P>0.05) without statistical significance while the three-factors model had significantly higher AUC compared with single ATIII (0.850 vs. 0.759; Z=1.7356; P<0.05). However, the sensitivity of single ATIII was 0.869, which was higher compared with sensitivity of SCr and constructed models. And adding ATIII could improve the sensitivity of constructed model, which was beneficial for physicians to evaluate risk of developing AKI in early stage.

Table II. Univariate logistic regression analysis of risk factors for acute kidney injury in included patients with traumatic brain injury.

Variables	Odds ratio	95% Confidence interval	P-value
Age, years	1.019	1.001-1.038	0.041
Male, n (%)	1.664	0.649-4.269	0.289
Systolic blood pressure, mmHg	0.995	0.982-1.009	0.514
Diastolic blood pressure, mmHg	0.989	0.969-1.009	0.274
Heart rate, min^{-1}	1.002	0.989-1.014	0.790
Body temperature,˚C	0.947	0.651-1.377	0.774
Respiratory rate, min^{-1}	1.000	0.942-1.063	0.991
Anisocoria	0.988	0.492-1.982	0.972
GCS	0.798	0.684-0.932	0.004
ISS	1.053	1.016-1.091	0.005
Glucose, mmol/l	1.130	1.050-1.215	0.001
White blood cell, 10^9/l	1.011	0.964-1.060	0.655
Neutrophil, 10^9/l	0.995	0.968-1.023	0.716
Lymphocyte, 10^9/l	0.642	0.328-1.255	0.195
Platelet, 10^9/l	0.994	0.989-1.000	0.035
Albumin, g/l	0.896	0.838-0.959	0.001
Hemoglobin, g/l	0.971	0.953-0.989	0.002
Fibrinogen, mg/l	0.738	0.592-0.921	0.007
D-dimmer, mg/l	1.016	0.991-1.042	0.218
Prothrombin time, sec	1.149	1.057-1.250	0.001
APTT, sec	1.600	1.357-1.886	<0.001
ATIII, %	0.943	0.922-0.965	<0.001
Blood urea nitrogen, mmol/l	1.056	1.004-1.112	0.035
Serum creatinine, μmol/l	1.011	1.005-1.017	<0.001
Acute liver dysfunction, n (%)	0.826	0.385-1.776	0.625
Marshall CT score	1.139	0.923-1.405	0.225
Subarachnoid hemorrhage, n (%)	1.071	0.543-2.111	0.843
Intraventricular hemorrhage, n (%)	0	0	0.999
Fresh frozen plasma, n (%)	5.955	2.878-12.32	<0.001
Fibrinogen transfusion, n (%)	1.803	0.725-4.485	0.205
Hydroxyethyl starch, n (%)	2.029	1.020-4.037	0.044
Red blood cell transfusion, n (%)	2.623	1.320-5.214	0.006
Mannitol, n (%)	1.097	0.482-2.498	0.826
Fructose glycerol, n (%)	1.568	0.569-4.318	0.385
Hypertonic saline, n (%)	0.294	0.128-0.673	0.004
Furosemide, n (%)	1.320	0.659-2.643	0.433
Vancomycin, n (%)	0.336	0.124-0.909	0.032
Meropenem, n (%)	0.825	0.293-2.324	0.716
Decompressive craniectomy, n (%)	1.927	0.974-3.814	0.060
Hematoma evacuation, n (%)	1.360	0.692-2.672	0.373

GCS, Glasgow Coma Scale; ISS, injury severity score; APTT, activated partial thromboplastin time; ATIII, antithrombin III.

Discussion

The present study found that ATIII level, SCr and transfusion of FFP were independently associated with the development of AKI after TBI. The logistic regression model constructed using these three factors was effective in predicting the development of AKI in early stages after TBI. Compared with the non-AKI group, AKI group had lower level of ATIII on admission. Based on findings of previous studies, the present study could conclude that a lower level of ATIII on admission was detrimental to maintenance of normal renal function and consequently promoted the development of AKI in patients with TBI.

The results of the present study showed that ATIII decreased after TBI and the decrease of ATIII was greater in

Table III. LASSO regression for selecting the strongest predictors for acute kidney injury in included patients with traumatic brain injury.

Variables	LASSO coefficient	Regression coefficient (β)
Serum creatinine	0.002	-0.244
ATIII	-0.017	0.224
Transfusion of FFP	0.586	0.309

FFP, Fresh frozen plasma; ATIII, antithrombin III; LASSO, least absolute shrinkage and selection operator.

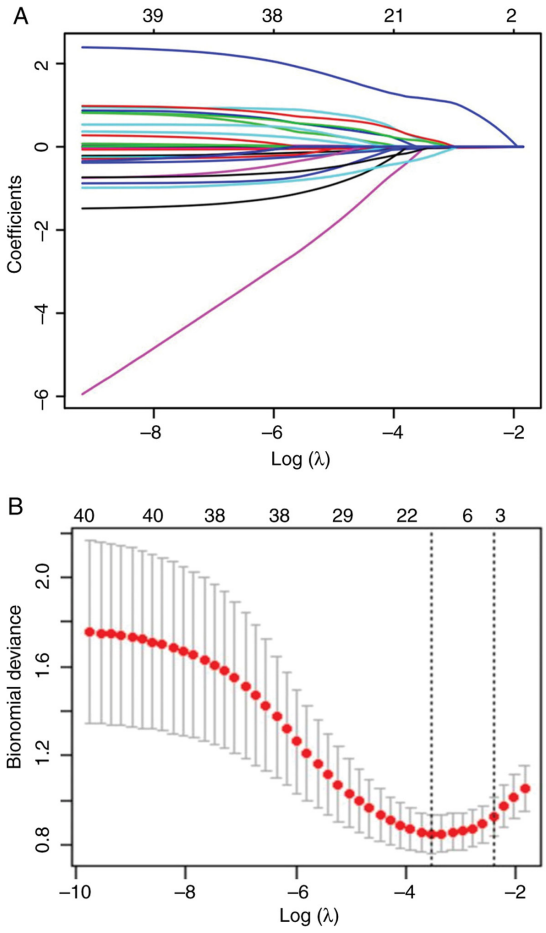

Figure 2. Risk predictors explored by the least absolute shrinkage and selection operator (LASSO) binary logistic regression analysis. (A) The risk predictors selection using the least absolute shrinkage and selection operator (LASSO) binary logistic regression analysis. The two dotted vertical lines mark the optimal values by minimum criteria and 1-s.e. criteria. The three variables were selected by LASSO binary logistic regression analysis. (B) LASSO coefficient profiles of the 39 variables. LASSO, least absolute shrinkage and selection operator.

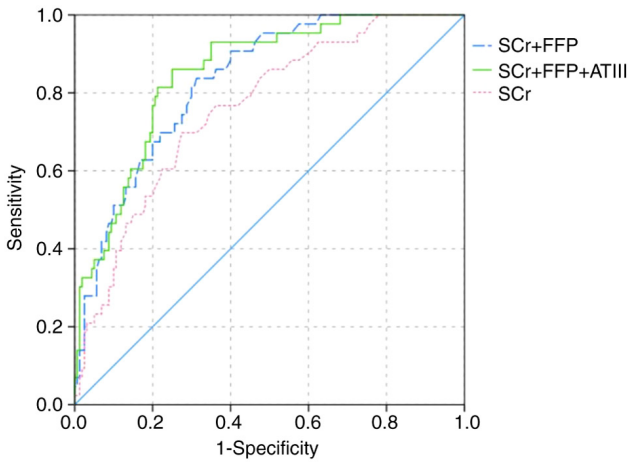

Figure 3. Receiver operating characteristic curve of single ATIII and constructed predictive models for predicting AKI in included TBI patients. The AUC value of ATIII, serum creatinine, two-factors predictive model and three-factors predictive model was 0.759 (0.674-0.844), 0.760 (0.684-0.836), 0.831 (0.770-0.891) and 0.850 (0.792-0.909), respectively. ATIII, antithrombin III; AKI, acute kidney injury; TBI, traumatic brain injury; AUC, area under the receiver operating characteristic curve; Scr, serum creatinine; FFP, fresh frozen plasma.

the AKI group than the non-AKI group. It was demonstrated that the prevalence of coagulopathy ranged from 12.5 to 45.7% in patients with TBI (26-29). Through initiating the extrinsic coagulation pathway, the tissue factor released from local injured brain tissue can promote the development of disseminated intravascular coagulation, which manifests as early hypercoagulation and subsequent fibrinolysis (30-33). As a crucial component of natural anticoagulation, ATIII can neutralize increased production of factor Xa and coagulation enzymes, including thrombin (factor IIa) and plasmin (34,35). The reactive center of ATIII is cleaved by thrombin and then irreversibly combined with thrombin to form an enzyme-inhibitor complex which is quickly cleared from the circulation (35). In addition to increased consumption, reduced synthesis due to the impaired liver function may also lead to the decreased ATIII level. The impaired liver function in patients with TBI can be attributable to the commonly existing systemic inflammatory response with elevated inflammatory cytokines level that promoted the hepato-cellular injury (36,37).

The renal-protective role of ATIII has been investigated through inhibiting local renal inflammation, oxidative stress activity and cell apoptosis (20). Both renal local inflammation and systemic inflammation response take part in the progress of AKI (38-41). ATIII can exert anti-inflammatory action in a renal ischemia-reperfusion injury model by inhibiting the release of proinflammatory cytokines from endothelial cells and subsequent chemokine mediated leukocytes infiltration, promoting the production of prostacyclin (PGI_2) (42,43). Previous studies showed that supplement of ATIII can reduce serum TNF-α concentration and consequently inhibit the expression levels of monocyte chemotactic protein 1 and intercellular cell adhesion molecule 1 in renal tissues (14,20). In addition, ATIII can exert anti-inflammatory effects by inducing the synthesis of PGI_2, which not only suppresses the proinflammatory effects of platelets, neutrophils and cytokines, but also restores renal cortical blood flow as an effective vasodilator (14,16,17,44,45). TBI can initiate the systemic inflammatory response syndrome and the release of various cytokines into the circulation, which is associated with non-neurological organ failure, such as AKI (46-48). Therefore, the present study considered that ATIII can also alleviate the progress of AKI in patients with TBI by mitigating

Table IV. Predictive value of ATIII and constructed models for predicting acute kidney injury after traumatic brain injury.

Variable	AUC	95% CI	SE	P-value	Sensitivity	Specificity	Best cut-off
SCr	0.760	0.684-0.836	0.039	<0.001	0.698	0.725	82.500
ATIII	0.759	0.674-0.844	0.043	<0.001	0.869	0.581	60.650
SCr + FFP	0.831	0.770-0.891	0.031	<0.001	0.837	0.687	0.127
SCr + FFP + ATIII	0.850	0.792-0.909	0.030	<0.001	0.860	0.750	0.170

AUC, area under the ROC curve; CI, confidence interval; SE, standard error; SCr, serum creatinine; ATIII, antithrombin III; FFP, fresh frozen plasma.

the detrimental effects of systemic inflammation and renal local inflammation.

Imbalanced oxidative stress has been confirmed as a critical pathogenetic factor which plays an important role in the development and progress of AKI (49-51). Therapeutic strategies targeting oxidative stress have attracted considerable attention (49). Previous studies have demonstrated that ATIII can alleviate the aggressive status of oxidative stress in renal tissue of rat models with AKI (14,17,20). The mitigation of increased malondialdehyde and decreased superoxide dismutase in injured renal tissue has been observed in rats that received a supplement of ATIII (52). The apoptosis of renal tubular epithelial cells is another key mechanism of AKI (53-55). It has been verified that ATIII are capable of reducing caspase-3 expression and increasing bcl-2 expression in rat models with AKI (20). Thus, the present study hypothesized the association between low ATIII level and AKI following TBI may also be mediated by oxidative stress and apoptosis.

Another possible explanation for the role of ATIII on alleviating renal injury may be the anticoagulative action. Previous studies hypothesized that thrombin generation can cause impairment to renal microcirculation and damage to tubular cells (53-55). In summary, the present study demonstrated that low ATIII level is independently related with the occurrence of AKI after TBI through the aforementioned mechanisms. Maintaining the appropriate ATIII level may be beneficial to prevent or lessen AKI after TBI. However, the specific and precise maintaining level of ATIII should be explored further. In addition, future studies involving animal models is worthwhile to design to confirm the potential aforementioned mechanism. In addition to ATIII, SCr and transfusion of FFP were independent risk factors of AKI after TBI in the present study. The clinical significance of SCr as an indication of glomerular filtration function has been acknowledged. The AUC value of only ATIII and SCr for predicting AKI in the present study was 0.759 and 0.760, respectively. Although the AUC value was comparable between ATIII and SCr, the sensitivity of ATIII was higher compared with SCr (0.869 vs. 0.698), which was beneficial for physicians to quickly identify patients with TBI and high risk of AKI. The SCr level may be influenced by blood loss, fluid dilution, muscle mass, nutritional status, age and sex and therefore may not reflect the acute change of estimated glomerular filtration rate sensitively. Additionally, the accuracy of BUN reflecting the renal function may also be disturbed by multiple factors including gastrointestinal bleeding, dehydration, inflammation and protein intake (56). The transfusion of FFP was also confirmed to be a risk factor for AKI in various types of patients, including those receiving liver transplantation (57-60). It has been demonstrated that FFP transfusion can trigger and even exacerbate an inflammatory, immunological and allergic reaction, which might aggravate the renal injury (61). The results of the present study showed that combining these factors together was more effective in predicting AKI compared with ATIII alone in patients with TBI.

The significant differences in blood glucose, prothrombin time, platelets, albumin, hemoglobin and fibrinogen do exist but are not present in the predictive model. This contradiction is due to the present study using the LASSO regression to develop the predictive model. The LASSO regression performs well in identifying predictors among a dataset that has numerous variables and a limited number of outcomes, and it can minimize the collinearity of selected risk factors and avoid overfitting of these factors. The clinical outcome of the present study that 43 TBI patients were identified with the AKI. Therefore, the present study did not use a traditional multivariate logistic regression model to explore the risk factors of AKI, but used LASSO to discover the strongest predictors of AKI from numerous potential risk factors. The blood glucose, prothrombin time, platelet, albumin, hemoglobin and fibrinogen levels showed significant differences; however, they did not show stronger predictive value compared with the three factors the present study revealed, including SCr, antithrombin III and FFP.

There were several limitations in the present study. Firstly, the present study was conducted in a single medical center and mainly included moderate to severe patients with TBI treated in NICU. Patients with history of surgery or severe infection within 4 weeks before TBI were also excluded. Therefore, selection bias may not be avoided. The findings of the present study should be further verified in future studies with larger sample sizes and more generalized patients with TBI. Secondly, the detailed dosage and infusion rate of drugs reducing ICP and blood products were not collected in the present study. The real confounding effects of these drugs may be weakened. Thirdly, underlying diseases, such as cardiovascular diseases, renal diseases and malignant tumor, were not collected as variables due to the low prevalence of them in the included patients. Finally, only levels of ATIII on admission but not subsequent fluctuation of ATIII were recorded; therefore, the present study could not evaluate the influence of ATIII changes on AKI development. Therefore, the conclusion

drawn from the present study should be verified in future studies.

In conclusion, ATIII is an easily obtained indicator of AKI after TBI. Decreased ATIII is associated with higher possibilities of AKI. Evaluating and avoiding decreased ATIII level may be helpful for clinicians to avoid possible occurrence of AKI in patients with TBI.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RRW and JGX conceived and designed the study, performed the statistical analysis and drafted the manuscript for intellectual content. RRW and MH acquired, analyzed and interpreted the data. RRW and MH confirm the authenticity of all the raw data. JGX reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the ethics committee of West China hospital, Sichuan University (approval number2021-1598) and has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Informed consent forms of each patients were legally obtained from themselves or their authorized families.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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