ORIGINAL RESEARCH

Incidence and Burden of Acute Kidney Injury among Traumatic Brain-Injury Patients

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Background: Acute kidney injury (AKI) has been occurs commonly in the clinical management of traumatic brain injury (TBI) patients and is correlated with outcomes in these patients. We designed this study to investigate the incidence, duration, stage, and burden of AKI among these patients.

Methods: A total of 419 TBI inpatients at our hospital were included in the study. We calculated the AKI burden, reflecting both stage and duration, and then analyzed associations among AKI occurrence, highest AKI stage, AKI duration, AKI burden, and outcomes with logistic regression analysis.

Results: Incidence of AKI among TBI patients was 19.8%. These patients' AKIs occurred mainly on the first day from admission (10.74%), and mostly developed stage 1 AKI (9.79%). Modes of AKI duration and burden in those with AKI were both 1. Multivariate logistic regression showed AKI occurrence (OR 3.792, p=0.004) and the highest AKI stage (OR 3.122, $p<0.001$) was significantly associated with mortality. Neither AKI duration (OR 1.083, $p=0.206$) nor AKI burden (OR 1.062, $p=0.171$) were associated with mortality. Incorporating AKI occurrence or highest AKI stage did not improve the predictive value of the constructed prognostic model.

Conclusion: The high-incidence period of AKI in TBI patients was the first 3 days after admission. AKI occurrence and highest AKI stage were associated with mortality, while AKI duration and AKI burden were not associated with mortality.

Keywords: acute kidney-injury duration, acute kidney-injury burden, traumatic brain injury, mortality
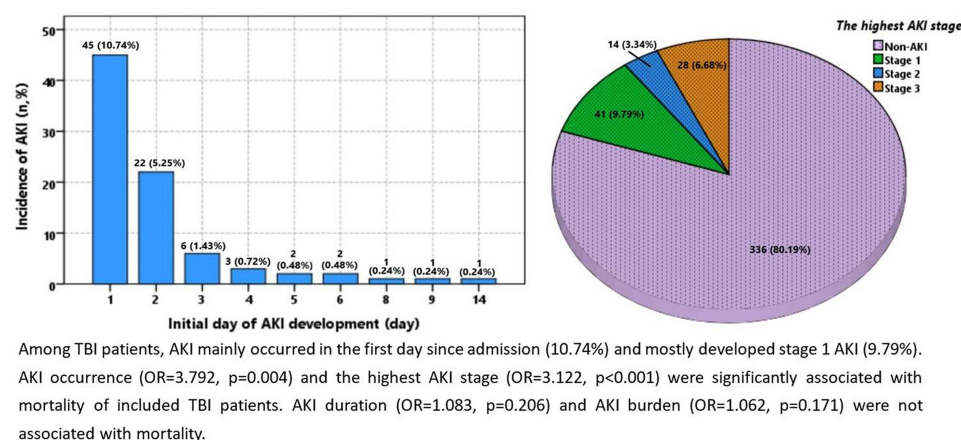
Introduction

Traumatic brain injury (TBI) is a severe public health issue involved a series of pathophysiological processes following the initial injury. Both initial head injury and subsequent secondary brain injury can aggravate extracranial organ dysfunction through complex mechanisms. The incidence of nonneurological organ dysfunction developing in TBI patients is 33%–89%.[1–4] Among various kinds of organ dysfunction, acute kidney injury (AKI) has attracted wide attention, due to its unfavorable effects on cerebral edema and prognosis of TBI patients. Both injury severity and inappropriate medical strategy can promote the development of AKI in TBI patients. Many factors play complex roles in the development of AKI after TBI, such as massive release of catecholamine transmitters, systemic inflammation, and iatrogenic factors, including massive drug doses reducing intracranial pressure and nephrotoxic antibiotics.[5–7]

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Graphical Abstract

Among TBI patients, AKI mainly occurred in the first day since admission (10.74%) and mostly developed stage 1 AKI (9.79%). AKI occurrence (OR=3.792, p=0.004) and the highest AKI stage (OR=3.122, p<0.001) were significantly associated with mortality of included TBI patients. AKI duration (OR=1.083, p=0.206) and AKI burden (OR=1.062, p=0.171) were not associated with mortality.

The incidence of AKI in TBI patients is 9.2%–24%.[8–11] There have been few studies to investigate the details of AKI duration and AKI stage and their correlation with mortality in TBI patients. Joint or additive effects of AKI duration and AKI stage on prognosis of TBI patients is worth exploring. In one study, the authors designed a novel index, the AKI burden, to indicate both AKI duration and AKI stage in aspecific critically ill patients.[12] We designed this study to investigate the incidence, timing, duration, stage, and burden of AKI among hospitalized TBI patients in detail and verify their association with prognosis of TBI patients.

Methods

Patients

Patients admitted to West China Hospital directly after a TBI between January 2015 and June 2019 were eligible for this study. Exclusion criteria were admission ≥6 hours after the injury, lacking relevant clinical variables, and existing chronic kidney disease. The flowchart for the inclusion process is presented in Figure 1. In sum, 419 patients were finally included. Thtudy was approved by the ethics committee of West China Hospital and performed in accordance with the Declaration of Helsinki. Informed-consent forms were regularly signed by patients themselves or their legally authorized representatives once admitted.

Data Collection

Demographic and clinical information — injury cause, vital signs on admission, Glasgow Coma Scale (GCS)

score on admission, injury severity score (ISS), laboratory tests, and radiology — were collected. Results of laboratory tests were obtained by analyzing the first blood sample collected once patients had been admitted to the emergency department. Five AKI-related variables were included in analysis: AKI development, initial day of AKI development, AKI duration, highest AKI stage, and AKI burden. AKI development was evaluated every day as per KDIGO guidelines using creatinine criteria.[13] As part of blood biochemistry testing, serum creatinine was measured and recorded every day. Initial day of AKI development was defined as the first day on which changes in serum creatinine met the KDIGO criteria. Day of admission was regarded as the first day. AKI duration was defined as the sum of days on which AKI lasted or progressed during the whole hospitalization. The end of AKI
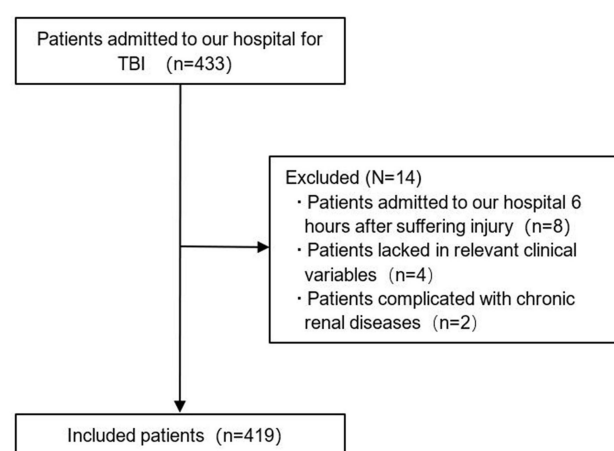

Figure 1 Flowchart of patient inclusion.

was defined as not meeting the KDIGO criteria. Highest AKI stage was defined as the most severe stage of AKI patients developed according to the KDIGO criteria. If patients did not develop AKI, their highest AKI stage was regarded as 0. AKI burden was calculated by multiplying AKI-stage score by the number of days in each stage. Non-AKI, stage 1, stage 2, and stage 3 were assigned scores of 0, 1, 2 and 3, respectively. The primary outcome of this study was mortality in TBI patients.

Statistical Analysis

The normality of variables was confirmed utilizing the Kolmogorov–Smirnov test. Normally distributed and abnormally distributed variables are shown in the form of means ± SD and medians (IQR), respectively. Categorical variables are presented as numbers and percentages. Independent Student's *t*-tests and Mann–Whitney *U* tests were performed to analyze the difference between groups of normally and abnormally distributed variables, respectively. Fisher's or χ^2 tests were used to compare differences among categorical variables. Univariate logistic regression was conducted to discover potential risk factors of mortality. Then, multivariate logistic regression was conducted to analyze the relationship between AKI-related variables and mortality through adjusting the confounding effects of factors significant on univariate regression (factors with $p<0.05$). To construct prognostic models incorporating AKI-related variables, stepwise forward multivariate logistic regression was applied. Receiver-operating characteristic (ROC) curves were drawn and area under the ROC curve (AUC) calculated to assess the prognostic value of single AKI-related variables and constructed models. *Z* tests were conducted to compare AUC differences among models. Two-sided $p<0.05$ was considered statistically significant. SPSS 22.0 and GraphPad (GraphPad Software, La Jolla, CA, USA) were used for all statistical analyses and drawing of figures.

Results
Baseline Characteristics

AKI incidence was 19.8% (Table 1). Compared with the non-AKI group, AKI group were older (47 years vs 41 years, $p=0.004$) and had higher ISSs (25 vs 22, $p<0.001$) and lower GCS scores (5 vs 6, $p<0.001$). Results of laboratory tests indicated that the AKI group had higher levels of glucose (12.24 mmol/L vs 8.97 mmol/L, $p<0.001$) and serum creatinine (128 μmol/L vs 65 μmol/L, $p<0.001$) than the non-AKI group. Platelets (74×10^9/L vs 116×10^9/L, $p<0.001$) and

hemoglobin (80 g/L vs 94 g/L, $p<0.001$) were both lower in the AKI group. Median initial AKI development was 1 (IQR 1–2) day since admission. Median AKI duration and AKI burden was 1 (IQR 1–3) and 2 (IQR 1–6), respectively. Median highest AKI stage was 2 (IQR 1–3). The AKI group had significantly higher mortality (84.3% vs 40.2%, $p<0.001$) and shorter hospital stay (7 vs 15 days, $p<0.001$) than the non-AKI group.

Distribution of AKI-Related Variables

Figure 2A showes the initial day of AKI development during hospitalization was mainly the first (10.74%) following admission. Incidence for the second and third days was 5.25% and 1.43%, respectively. As such, AKI following a TBI mainly developed in the 3 days following admission. Figure 2B shows that AKI duration during hospitalization for TBI was mostly 1 day (10%). Duration of 2 days and 3 days ranked second and third: 4.3% and 2.1%, respectively. Incidence of stage 1, 2, 3 AKI was 9.79%, 3.34%, and 6.68%, respectively (Figure 2C). Figure 2D shows AKI burden of 1 (7.2%), 2 (3.1%), and 3 (2.4%) patients with AKI.

Univariate Logistic Regression Analysis of Risk Factors of Mortality

Univariate logistic regression indicated that heart rate (OR 1.013, $p<0.001$), ISS (OR 1.108, $p<0.001$), glucose (OR 1.279, $p<0.001$), serum creatinine (OR 1.013, $p<0.001$), subdural hematoma (OR 2.886, $p<0.001$), subarachnoid hemorrhage (OR 1.825, $p=0.002$), and diffuse axonal injury (OR 1.829, $p=0.009$) were potential risk factors of mortality in TBI patients (Table 2). GCS (OR 0.597, $p<0.001$), platelet count (OR 0.991, $p<0.001$), and hemoglobin (OR 0.975, $p<0.001$) were negatively associated with increased mortality, and injury cause ($p=0.017$) was related withto mortality.

Association Between AKI-Related Variables and Mortality

Through multivariate logistic regression (enter method), we analyzed the association between four AKI related variables and mortality of TBI patients by adjusting the confounding effects of significant factors on univariate logistic regression. Results showed AKI occurrence (OR 3.792, $p=0.004$) and highest AKI stage (OR 3.122, $p<0.001$) were significantly associated with mortality, while AKI duration (OR 1.083, $p=0.206$) and AKI burden (OR 1.062, p=0.171) were not

Table 1 Baseline characteristics of TBI patients with and without AKI

	Overall (n=419)	Non-AKI (n=336, 80.2%)	AKI (n=83, 19.8%)	p
Age (years)	43 (25–57)	41 (24–54)	47 (36–60)	0.004
Male sex	320 (76.4%)	253 (75.3%)	67 (80.7%)	0.289
Injury cause				0.006
Motor-vehicle accident	262 (62.5%)	205 (61.0%)	57 (68.7%)	
Fall	84 (20.0%)	67 (19.9%)	17 (20.5%)	
Stumble	46 (11.0%)	37 (11.0%)	9 (10.8%)	
Other	27 (6.4%)	27 (8.0%)	0	
Vital signs on admission				
Systolic blood pressure (mmHg)	120 (106–138)	121 (106–138)	118 (103–144)	0.400
Diastolic blood pressure (mmHg)	72±16.51	73±15.29	69±20.46	0.074
Heart rate (bpm)	100 (81–120)	98 (80–118)	104 (86–124)	0.120
Body temperature (°C)	36.7 (36.5–37.0)	36.7 (36.5–37.0)	36.8 (36.3–37.1)	0.681
Anisocoria	116 (27.7%)	96 (28.6%)	20 (24.1%)	0.409
GCS	6 (5–9)	6 (5–10)	5 (4–6)	<0.001
ISS	25 (16–25)	22 (13–25)	25 (16–29)	<0.001
Laboratory tests				
Glucose (mmol/L)	9.64 (7.04–13.16)	8.97 (6.64–12.50)	12.24 (9.00–17.15)	<0.001
Platelets (10^9/L)	105 (68–165)	116 (74–176)	74 (45–111)	<0.001
Hemoglobin (g/L)	90 (76–110)	94 (78–112)	80 (72–90)	<0.001
Serum creatinine (μmol/L)	71 (53–96)	65 (49–83)	128 (86–209)	<0.001
Radiology				
Epidural hematoma	43 (10.3%)	38 (11.3%)	5 (6.0%)	0.133
Subdural hematoma	101 (24.1%)	78 (23.2%)	23 (27.7%)	0.397
Subarachnoid hemorrhage	230 (54.9%)	184 (54.8%)	46 (55.4%)	0.914
Diffuse axonal injury	103 (24.6%)	76 (22.6%)	27 (32.5%)	0.067
AKI-related variables				
Initial day of AKI development	0	—	1 (1–2)	<0.001
AKI duration	0	—	1 (1–3)	<0.001
Highest AKI stage	0	—	2 (1–3)	<0.001
AKI burden	0	—	2 (1–6)	<0.001
Mortality	205 (48.9%)	135 (40.2%)	70 (84.3%)	<0.001
Length of ICU stay (days)	3 (1–3)	4 (1–18)	2 (1–11)	0.997
Length of hospital stay (days)	12 (5–12)	15 (5–31)	7 (3–14)	<0.001

Abbreviations: AKI, acute kidney injury; GCS, Glasgow coma scale; ISS, injury- severity score.

(Table 3). Figure 3A–D showed detailed mortality differences regarding AKI occurrence, AKI duration, AKI stage, and AKI burden. The cutoff point for grouping of AKI duration and AKI burden was based on quartiles of these two variables in the AKI group.

Prognostic Value of AKI-Related Variables and Constructed Logistic Models

From the ROC curve, we evaluated the prognostic value of AKI-related variables and found the AUC of single AKI-related variables did not differ from one other. As shown in Table 4, the AUC of AKI occurrence, AKI duration, the highest AKI stage, and AKI burden was 0.640, 0.643, 0.643, and 0.644, respectively. Due to the insignificant association between AKI duration, AKI burden, and mortality, we constructed only prognostic models incorporating AKI occurrence or highest AKI stage. The forward stepwise multivariate logistic regression indicated GCS, glucose, SDH (subdural hematoma), AKI occurrence, or highest AKI stage were independently associated with mortality. We constructed a prognostic logistic model incorporating these factors. Comprising GCS, glucose,
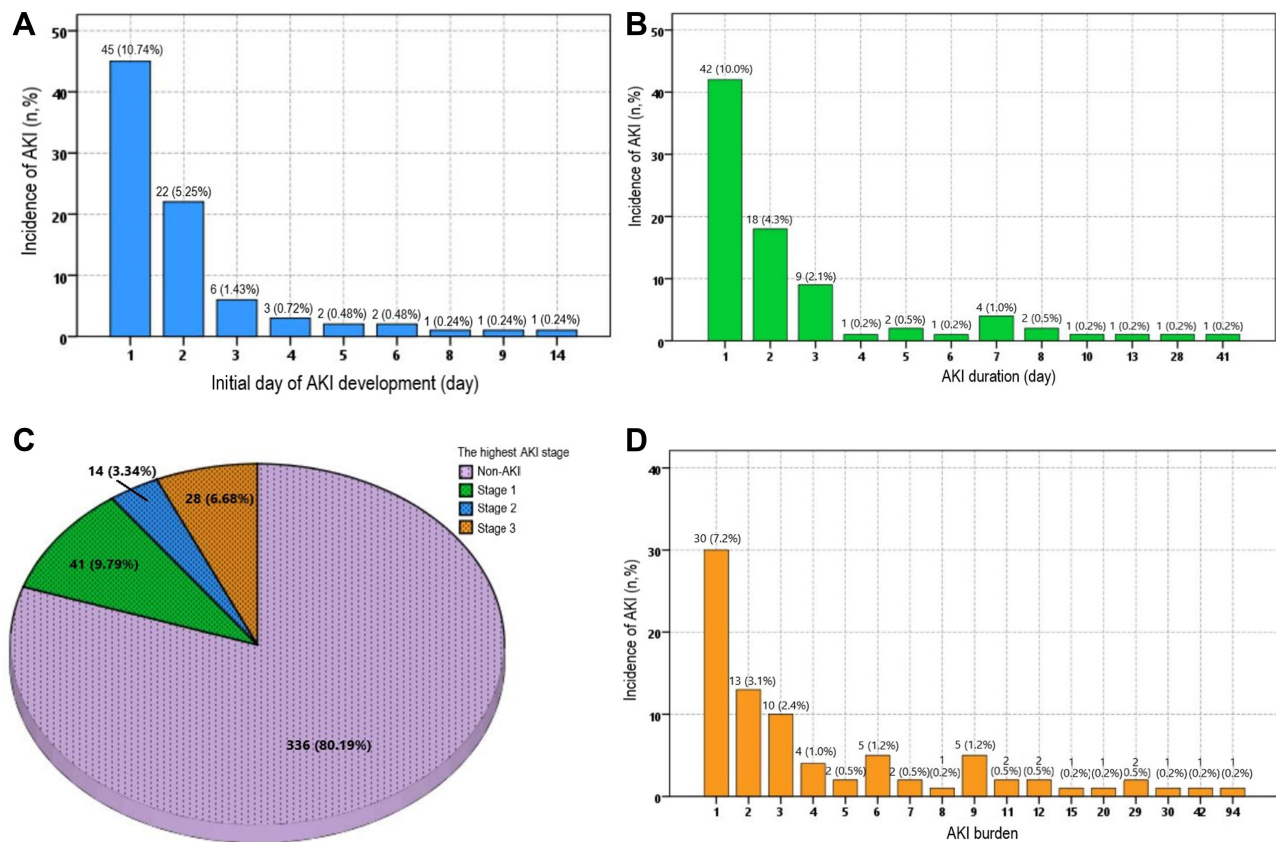
Figure 2 (**A**) Initial day of AKI development during hospitalization in TBI patients. This was principally on the first day (10.74%). (**B**) Distribution of AKI duration during hospitalization in TBI patients, most commonly 1 day (10%). (**C**) Distribution of highest AKI stage during hospitalization in TBI patients. Stage 1, 2, and 3 AKI incidence was 9.79%, 3.34%, and 6.68%, respectively. (**D**) Distribution of AKI burden during hospitalization in TBI patients, most commonly stage 1 (7.2%).

and SDH, model 1 had an AUC of 0.860 (Table 4) (Figure 4). Adding AKI occurrence or highest AKI stage to Model 1, the model 2 and model 3 had AUCs of 0.880 and 0.885, respectively. Z tests indicated that the AUCs of model 2 and model 3 were not significantkly higher than model 1 (0.880 vs 0.860, $Z=0.8305$, $p>0.05$; 0.885 vs 0.860, $Z=1.0381$, $p>0.05$).

Discussion

TBI patients commonly develop nonneurological dysfunctions during hospitalization, due to a series of pathophysiological processes, including catecholamine surge and local and systemic inflammation.[6,7] Characterized as massive releases of adrenergic transmitters, the catecholamine surge after TBIs excessively activates the renin–angiotensin–aldosterone system, which in turn promotes renal dysfunction.[6,14] Many inflammatory mediators released from damaged cerebral tissue, such as IL6 and CRP, promote systemic inflammation involved in extracranial organ damage, including renal dysfunction.[15,16] Some iatrogenic factors may also play significant roles in the development

of AKI after TBI. Massive doses of mannitol and hypertonic saline can both increase the risk of AKI development.[17–19] Nephrotoxic antibiotics, such as vancomycin, are sometimes used in medical centers for treating nosocomial infections during hospitalization.

AKI incidence among our TBI patients was 19.8%, consistent with previous studies.[8–11] Variations in incidence of AKI in previous studies on TBI may be attributable to the severity of brain injury, complicated extracranial injuries, history of underlying diseases, and diversity of clinical practice at different medical centers. Few studies have specifically investigated the distribution of initial day of AKI development. We found that 17.42% of patients had AKI onset TBI within the first 3 days after admission, which accounted for 87.95% (73 of 83) of patients with AKI. The median initial day was 1 (IQR 1–2), similar to a study in which reported AKI developed early after ICU admission, with a median of 2 (IQR 1–4) days.[20] AKI is an early nonneurological complication that mainly occurs within 7 days after brain injury. The special early phase of AKI development may be due to concomitant

Table 2 Univariate logistic regression analysis for risk factors of mortality in TBI patients

	OR	95% CI	p
Age (years)	1.004	0.995–1.013	0.403
Male sex	0.873	0.556–1.371	0.556
Injury cause			0.017
Motor-vehicle accident	1	Reference	
Fall	0.584	0.354–0.961	0.034
Stumble	0.858	0.458–1.606	0.632
Other	0.300	0.123–0.735	0.008
Systolic blood pressure (mmHg)	0.993	0.986–1.001	0.080
Diastolic blood pressure (mmHg)	0.989	0.978–1.001	0.071
Heart rate (bpm)	1.013	1.006–1.021	<0.001
Body temperature (°C)	0.825	0.661–1.030	0.089
Anisocoria	0.689	0.447–1.061	0.091
GCS	0.597	0.533–0.668	<0.001
ISS	1.108	1.080–1.136	<0.001
Glucose (mmol/L)	1.279	1.204–1.358	<0.001
Platelets (10^9/L)	0.991	0.988–0.994	<0.001
Hemoglobin (g/L)	0.975	0.967–0.984	<0.001
Serum creatinine (μmol/L)	1.013	1.007–1.018	<0.001
Epidural hematoma	0.898	0.477–1.690	0.738
Subdural hematoma	2.886	1.796–4.637	<0.001
Subarachnoid hemorrhage	1.825	1.236–2.695	0.002
Diffuse axonal injury	1.829	1.164–2.876	0.009

Abbreviations: GCS, Glasgow Coma Scale; ISS, injury-severity score.

pathophysiological processes in the early phase following injury, including massive bleeding–induced hypoperfusion, systemic inflammation caused by initial and secondary brain injury, and rapid and heavy use of hyperosmotic drugs once admitted.[5,21–23] This fact underlines the need to evaluate risk of developing AKI and consequently adjust treatment decisions for TBI patients as early as possible. Future studies need to be conducted to discover risk factors of AKI in the prehospital period and construct valuable risk scores based on these factors. Among the three AKI stages, stage 1 accounted for a majority of TBI patients with AKI,

consistent with previous studies.[10,11,20] Additionally, AKI stage was significantly associated with mortality in patients in our study. A higher AKI stage, indicating worse renal function, may affect prognosis by reflecting injury severity and aggravating brain edema and and hence prescription of nephrotoxic antibiotics to prevent infection.

In our study, AKI duration of 1 day accounted for 50.60% (42 of 83) of TBI patients with AKI, which indicated most AKI events in TBI were transient. This may partially be due to close attention to serum-creatinine levels and subsequent treatment adjustment,

Table 3 Characteristics of AKI-related variables and their association with mortality on univariate and multivariate logistic regression analysis

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
AKI occurrence	8.017	4.266–15.065	<0.001	3.792	1.540–9.341	0.004
AKI duration	1.512	1.187–1.926	0.001	1.083	0.957–1.225	0.206
Highest AKI stage	3.307	2.166–5.049	<0.001	3.122	1.669–5.837	<0.001
AKI burden	1.261	1.099–1.447	0.001	1.062	0.974–1.158	0.171

Note: Multivariate logistic regression adjusted for GCS, ISS, injury cause, heart rate, glucose, platelets, hemoglobin, serum creatinine, subdural hematoma, subarachnoid hemorrhage, and diffuse axonal injury.
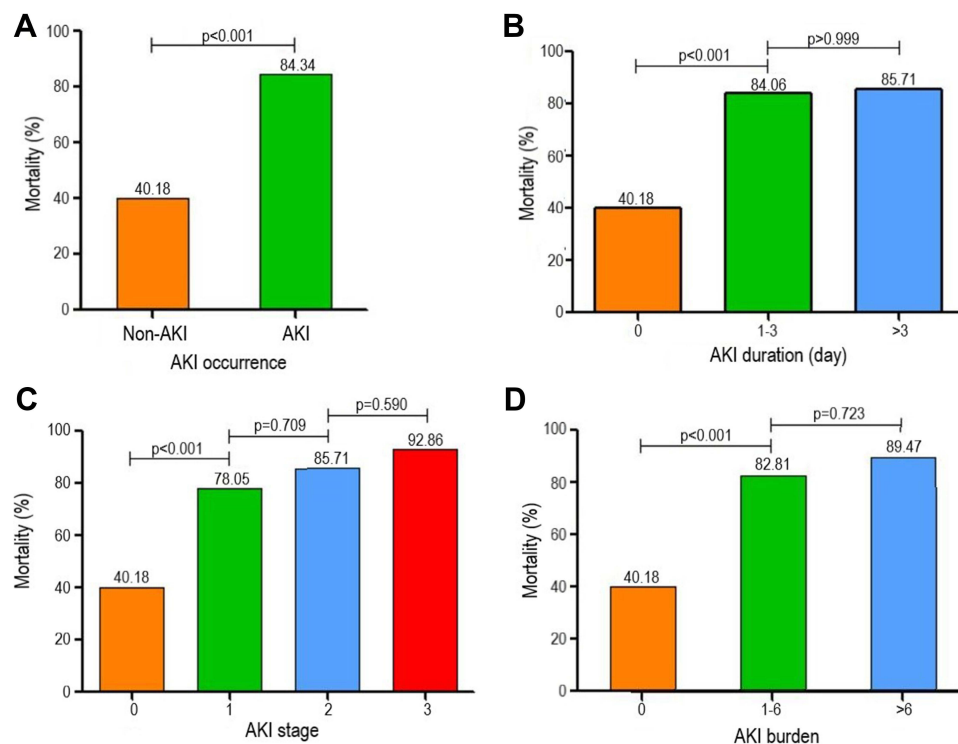
Figure 3 (**A**) Mortality comparison of TBI patients grouped by AKI occurrence. (**B**) Mortality comparison of included TBI grouped by AKI duration. Bonferroni corrected α was 0.05/3 (p=0.0167). (**C**) Mortality comparison of TBI patients grouped by the highest AKI stage. Bonferroni corrected α was 0.05/6 (p=0.0083). (**D**) Mortality comparison of TBI patients grouped by AKI burden. Bonferroni corrected α was 0.05/3 (p=0.0167).

such as changing hypertonic drugs and avoidance of nephrotoxic antibiotics. In addition, AKI duration was not correlated with mortality after adjusting for confounding effects. Most of previous studies have confirmed the association between prolonged AKI duration and poorer prognosis in various kinds of patients, including diabetics, those undergoing cardiac surgery, and the critically ill patients.[20,24–27] However, another two studies verified that AKI duration was not associated with mortality in critically ill patients.[28,29] We considered that the correlation between AKI duration and outcome may be confounded by illness severity, demographic characteristics,

underlying diseases, and AKI stage. Compared with transient AKI, persistent AKI may more likely present as high-stage AKI due to the ongoing process of high-stage AKI development. Therefore, the association between AKI duration and outcomes should be viewed with cautioun, taking into account the aforementioned confounding factors, especially AKI stage.

Calculated by the sum of each AKI stage multiplied by duration at each stage, AKI burden could collectively reflect the degree and duration of AKI. One study found that a prognostic model including AKI burden outperformed models incorporating AKI presence, severity, or

Table 4 Predictive value of single lactate and the logistic model

	AUC	95% CI	Sensitivity	Specificity
AKI occurrence	0.640	0.587–0.694	0.341	0.939
AKI duration	0.643	0.590–0.696	0.341	0.939
Highest AKI stage	0.643	0.590–0.696	0.341	0.939
AKI burden	0.644	0.591–0.697	0.341	0.939
Model 1	0.860	0.825–0.895	0.858	0.724
Model 2	0.880	0.848–0.912	0.912	0.720
Model 3	0.885	0.854–0.916	0.907	0.720

Notes: Model 1 composed of GCS, glucose, and SDH; model 2 composed of GCS, glucose, SDH, and AKI; model 3 composed of GCS, glucose, SDH, and highest AKI stage.
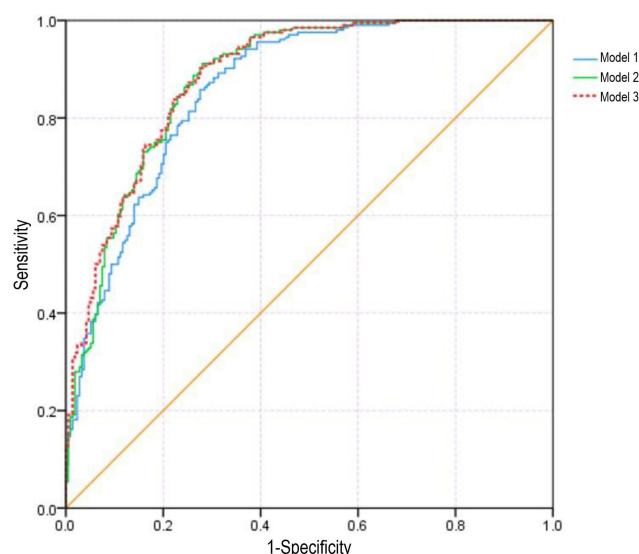
Figure 4 Receiver-operating characteristic curve of multivariate logistic models incorporating AKI-related variables for predicting mortality of TBI patients. Model 1 was composed of GCS, glucose, and SDH, with AUC of 0.860. Model 2 was composed of GCS, glucose, SDH, and AKI, with AUC of 0.880. Model 3 was composed of GCS, glucose, SDH, and highest AKI stage, with AUC of 0.885.

duration in critically ill patients.[12] Another study revealed that the AUC of a prognostic model incorporating AKI duration and stage together was higher than one including AKI stage alone, but not including AKI duration alone in critically ill patients after non–cardiac surgery.[30] Similarly to findings of that study, our results indicated AKI duration and burden were not significantly associated with mortality in TBI patients. The AUC of AKI burden in our study was 0.644, higher than the 0.643 for AKI duration or highest AKI stage alone, yet without statistical significance. Perhaps studies with larger samples could further verify differences in AUCs among AKI burden, duration, or highest stage. Due to the insignificance of association between AKI duration and mortality in our study, the AKI burden calculated by multiplying AKI stage with AKI duration showed no statistical significance in relation to mortality on multivariate logistic regression either.

The prognostic model composed of GCS, SDH, and glucose had an AUC of 0.860, though AKI occurrence and highest AKI stage were associated with mortality on multivariate logistic regression. Incorporating AKI occurrence or highest AKI stage did not improve the predictive value of the original three-factor model, which means AKI did not provide additive prognostic value for outcomes. The insignificant statistical difference in AUC between the three factors model and AKI-included models may be due to the insufficient sample size in our study. Further studies with

larger samples could be done to verify the additive prognostic value of AKI on outcomes of TBI patients.

This study has several limitations. Firstly, it was a single-center study with moderate sample size. Therefore, selection bias was inevitable and the generalization of conclusions is limited. Future studies conducted in multiple centers with larger samples need to be conducted to verify our conclusions. Secondly, we could not obtain the baseline value of serum creatinine before TBI, due to the retrospective nature of the study and characteristics of acute illness. This limitation is hard to avoid in research on TBI. The inclusion criterion of the time limit in this study was 6 hours after injury to include generalized and broad TBI patients as much as possible. However, the interval between suffering initial injury and obtaining blood samples could influence the baseline serum-creatinine level. Thirdly, AKI was diagnosed based on KDIGO guidelines using only creatinine criteria. Due to the lacke of records on urine output in the electronic system in our hospital, we could not evaluate AKI according to urine output and thus may have underestimated the prevalence of AKI among our patients.

Conclusion

The first three days after admission was the high-incidence period of AKI in TBI patients. AKI occurrence and highest AKI stage were associated with mortality in TBI patients, while AKI duration and AKI burden were not associated with mortality. Future studies with larger samples are needed to verify our conclusions.

Ethics

This study was approved by the ethics committee of West China Hospital (approval ID 2018-359) and performed based on the Declaration of Helsinki. Informed-consent forms were signed by the patients themselves or their legally authorized representatives before study commencement.

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Disclosure

The authors report no conflicts of interest in this work.

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