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Risk factors for acute kidney injury in patients with traumatic brain injury: a single-centre retrospective cohort study with an exploratory external validation in MIMIC-IV

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Abstract

Background

Acute kidney injury (AKI) is a frequent serious complication of traumatic brain injury (TBI) in the ICU, yet its modifiable risk factors are incompletely characterised. We aimed to identify independent AKI risk factors after TBI and test their reproducibility in an external cohort.

Methods

We retrospectively included 255 TBI patients admitted to the neurosurgical ICU of the Affiliated Hospital of Nantong University (March 2021–August 2024). An external cohort of 120 ICU patients with TBI was drawn from MIMIC-IV. AKI was defined by KDIGO criteria. Independent risk factors were identified by univariable and multivariable logistic regression (odds ratios per 1-SD increase) and their reproducibility was assessed in the external cohort; model discrimination was assessed in both cohorts.

Results

AKI occurred in 47.1% (120/255) of the local cohort and 24.2% (29/120) of the external cohort. In multivariable analysis, severe TBI (GCS ≤ 8; aOR 9.42, 95% CI 3.74–23.69), loop-diuretic use within 48 h (aOR 3.93, 95% CI 1.74–8.87) and elevated CK-MB (aOR 1.78, 95% CI 1.30–2.45) were positively associated with AKI, whereas greater first-day fluid balance (aOR 0.60, 95% CI 0.44–0.81) and mannitol use within 48 h (aOR 0.37, 95% CI 0.16–0.87) were inversely associated (all $P < 0.05$); neither 72-h magnesium nadir nor pupillary abnormality was significant. These associations were not replicated externally (all $P > 0.05$, including Firth penalisation); external patients were far less severely injured (10.0% vs 81.6% severe TBI [GCS ≤ 8]). An exploratory secondary prediction-model analysis likewise showed no external discrimination (AUC 0.531, 95% CI 0.399–0.662; see Supplementary Material), supporting non-replication rather than refutation.

Conclusions

In the local cohort, AKI after TBI was associated with severe TBI, loop-diuretic use and myocardial injury markers, with several fluid-management factors inversely associated. Neither the risk-factor associations nor the prediction model generalised externally, indicating centre specificity; multicentre prospective validation is warranted.

Background

Acute kidney injury (AKI) is a common and severe complication in patients with traumatic brain injury (TBI) admitted to the intensive care unit (ICU), and is closely associated with prolonged hospital stay,

long-term chronic kidney disease, and increased mortality [1]. Because of the interplay between multiple pathophysiological processes in TBI (including intracranial pressure management, fluid resuscitation, osmotic diuretics, and neuroendocrine disturbances), the mechanisms of AKI differ from those in general ICU patients, and its risk-factor profile remains incompletely understood [2–4].

Most existing studies rely on single-centre, small-sample data and have given insufficient attention to TBI-specific modifiable factors (such as osmotic diuretics, early fluid balance, and myocardial injury markers). Moreover, most prediction models lack external validation, and their generalisability remains uncertain. Therefore, identifying the independent risk factors for AKI in TBI patients and validating their reproducibility in an independent external cohort is essential for the early identification of high-risk patients and for informing risk awareness.

Drawing on a single-centre retrospective cohort, this study used multivariable logistic regression to identify the independent risk factors for AKI after TBI and the MIMIC-IV external cohort to validate these associations, and reported the internal and external discrimination of the resulting prediction model, to inform clinical risk stratification. We hypothesised that severe TBI, early loop-diuretic use, and elevated myocardial injury markers are independently and positively associated with AKI, whereas active early fluid management and mannitol use are inversely associated, and we tested the reproducibility of these associations in an independent external cohort.

Methods

2.1 Study design and participants

This was a single-centre, electronic medical record-based retrospective cohort study, reported in accordance with the STROBE statement [5]. For the local cohort, TBI patients first admitted to the NSICU of the Affiliated Hospital of Nantong University between March 2021 and August 2024 were screened via the hospital information system (HIS). The exclusion criteria were: age < 18 years; pre-existing renal disease; congestive heart failure or previous cardiac surgery; history of malignancy; history of craniocerebral surgery; time from injury to admission > 24 h; and an ICU stay < 48 h. Of 461 screened patients, 205 were excluded and 256 patients were enrolled. One patient was excluded because of a missing outcome (AKI) variable, leaving a final analysis cohort of 255 patients (Fig. 1).

External validation cohort: drawn from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database [6], in which ICU patients with TBI aged ≥ 18 years were screened. The exclusion criteria were: pre-existing renal disease; congestive heart failure or previous cardiac surgery; history of malignancy; history of craniocerebral surgery; multiple ICU admissions; absence of relevant renal measurements within 24 h of ICU admission; an ICU stay < 48 h; and ICU types other than the NSICU. Of 5940 screened patients, 5820 were excluded and 120 patients were finally included, serving as the external validation cohort.

2.2 AKI definition, outcome, and variables

AKI was defined according to the KDIGO guideline [7] as an increase in serum creatinine (SCr) by ≥ 0.3 mg/dL within 48 h, an increase to ≥ 1.5 times the baseline value within 7 days, or urine output < 0.5 mL/kg/h for ≥ 6 h. The outcome was the occurrence of AKI at any time during hospitalisation (yes/no). Baseline SCr was defined as the lowest value measured within 48 h after admission; if no measurement was available within 48 h, the lowest value within 7 days was used, or otherwise the first admission value. Both the SCr and urine-output criteria were applied in the local cohort; the external MIMIC cohort definition relied mainly on the SCr criterion (with baseline creatinine at ICU admission or the MDRD-estimated steady-state value) because urine-output records were incomplete, which may contribute to its lower AKI incidence.

Candidate predictors were derived from baseline and early (first 48–72 h) variables in the electronic medical record. A final set of seven predictors was selected from clinically plausible candidates and informed by univariable screening ($P < 0.05$) together with clinical/biological plausibility: first-day fluid balance, loop-diuretic use, mannitol use, severe TBI, pupillary abnormality, CK-MB and the 72-h magnesium nadir. Because some of these variables (loop-diuretic use, mannitol use, and first-day fluid balance) were interventions administered after ICU admission, their temporal precedence relative to AKI onset is not fully assured, and the observed relationships should be interpreted as associations rather than established causal risk factors.

They were defined as follows: first-day fluid balance was the difference between intake and output within the first 24 h of admission; the 72-h magnesium nadir was the lowest magnesium value among serial tests within 72 h; CK-MB was the highest value within 72 h; pupillary abnormality was defined operationally from the admission neurological examination as unequal pupils (anisocoria) or bilaterally fixed/dilated pupils (coded as equal = 0, unequal = 1, bilaterally fixed/dilated = 2, unrecordable = 3); unrecordable pupils (code 3) were included as abnormal in the primary analysis, and the influence of this coding choice was examined in a sensitivity analysis reported in the Results; severe TBI was defined as Glasgow Coma Scale (GCS) ≤ 8, using the lowest GCS recorded within the first 24 h (the pre-sedation or earliest value in intubated/sedated patients).

In the external MIMIC-IV cohort, GCS was taken as the first recorded value after ICU admission, using the recorded total score or, where the total was absent, the sum of the eye, verbal and motor components, and because GCS in that database is frequently documented after intubation and sedation the recorded values were used as such, so severity classification there may be influenced by sedation. Loop-diuretic and mannitol use were recorded as present if administered within the first 48 h of admission; in the external cohort these drugs were identified from the MIMIC-IV medication (inputevents) records within the first 48 h after ICU admission. Laboratory indicators (SCr, magnesium, CK-MB) were measured by the hospital's automated biochemistry analyser; the corresponding indicators in MIMIC-IV were derived from its laboratory module with units converted to a uniform scale. Magnesium was modelled as the 72-h nadir, whereas the remaining descriptive statistics used the single admission value.

Because AKI was assessed as a yes/no outcome at any time during hospitalisation while several predictors were measured within the first 48–72 h, the temporal ordering between early-measured predictors (peak CK-MB, 72-h magnesium nadir, diuretic/mannitol exposure) and AKI onset cannot be strictly guaranteed for patients developing AKI very early; a landmark sensitivity analysis was therefore not possible: this dataset was assembled as an aggregated analytic extract in which serial measurements were summarised (for example as maximum, minimum and mean values) and individual measurement timestamps were not retained, so the exact time of AKI onset could not be reconstructed; this is flagged as a limitation (see Limitations).

2.3 Statistical methods

For continuous variables, normality was assessed using the Shapiro–Wilk test: when both groups were normally distributed ($P > 0.10$), data were described as mean ± standard deviation and compared using Welch's t-test; otherwise, data were described as median (P25–P75) and compared using the Mann–Whitney U test. Categorical variables were described as frequencies and proportions, and compared using the χ^2 test, with Fisher's exact test or Yates' correction applied when the expected frequency was < 5.

Risk-factor analysis was performed in the full local cohort (n = 255) using univariable and multivariable logistic regression, with the seven predictors entered into the multivariable model; odds ratios were reported per 1-SD increase for continuous variables and as “present versus absent” for categorical variables, to identify independent risk factors. Because of listwise deletion across the seven predictors, the multivariable model was estimated in 249 complete cases (of 255); univariable analyses used all 255 patients. Sex was deliberately excluded from the primary seven-factor model to keep the focus on the seven TBI-specific predictors; the events-per-variable ratio was approximately 17 (ample capacity), and sex was instead evaluated in sensitivity analyses. Forced together with total SOFA score and vasoactive-drug use, sex was independently associated with AKI ($P = 0.03$) whereas SOFA ($P = 0.19$) and vasoactive-drug use ($P = 0.47$) were not; re-fitting the primary model with sex included changed the seven retained factors by < 6% (e.g., severe TBI aOR 9.42 → 9.38; loop-diuretic 3.93 → 3.84), confirming that its exclusion did not bias the primary estimates. To enable independent internal validation of the prediction model, the full cohort was additionally divided into a training set (n = 178) and an internal validation set (n = 77) using 7:3 stratified random sampling (seed = 42), used solely for model training and assessment of internal discrimination; effect estimates for the risk factors were based on the full cohort. The external cohort used the same variables and coding wherever available to validate the associations. Multicollinearity among predictors was assessed with the variance inflation factor (all VIFs < 2.0, maximum 1.84 for SOFA, indicating no concerning collinearity). The logit-linearity assumption for continuous predictors was assessed with quadratic tests; no significant deviation was found for first-day fluid balance ($P = 0.12$), CK-MB ($P = 0.26$) or 72-h magnesium nadir ($P = 0.94$).

Prediction models (multivariable logistic regression [MLR], random forest [RF] and XGBoost) were additionally developed in accordance with the TRIPOD statement [8]; they were built on the training set (hyperparameters tuned by 5-fold cross-validation) and then evaluated without refitting on the internal

validation set (n = 77) and the external cohort (n = 120), with performance summarised by the area under the receiver operating characteristic curve (AUC), reported with DeLong 95% confidence intervals; a two-sided $P < 0.05$ was considered statistically significant and variable importance was derived from the trained ensembles (see Supplementary Material). A generic SOFA score was additionally evaluated post hoc as an exploratory benchmark of cross-centre transportability. These prediction models represent an exploratory secondary analysis performed alongside the primary risk-factor analysis.

This study used a complete-case approach for missing data; the missingness rate for each variable in the local cohort was < 5%. In the external cohort, CK-MB was missing in 111 of 120 cases (92.5%), and was therefore excluded from the external multivariable model; the relevant results are discussed only in the limitations section.

Statistical analyses were performed using R (version 4.6.1; used for descriptive statistics, univariable and multivariable logistic regression, Firth-penalised logistic regression, and Love plots) and Python (statsmodels, scikit-learn, and xgboost; used for data management and the random-forest and XGBoost models).

To present model performance and baseline comparability more comprehensively, several supplementary analyses are provided in the Supplementary Material: the calibration curves of the prediction model (Supplementary Figure S1); a Love plot of the standardised mean differences of baseline variables between the AKI and non-AKI groups (Supplementary Figure S2); the distribution of the 72-h magnesium nadir between the two groups (Supplementary Figure S3); a Love plot comparing the local and external cohorts (Supplementary Figure S4); internal and external discrimination of the prediction models (Supplementary Table S1); calibration metrics of the multivariable logistic model (Supplementary Table S2); external-cohort baseline characteristics (Supplementary Table S3); Firth-penalised external logistic estimates (Supplementary Table S4); and the STROBE and TRIPOD reporting checklists.

Results

3.1 Participant screening and baseline characteristics

The participant screening and model-development flow is shown in Fig. 1. For the local cohort, 461 patients with TBI admitted to the NSICU for the first time were screened via the hospital information system between March 2021 and August 2024; after applying the exclusion criteria (age < 18 years, n = 11; pre-existing renal disease, n = 8; congestive heart failure or previous cardiac surgery, n = 19; history of malignancy, n = 14; history of craniocerebral surgery, n = 67; time from injury to admission > 24 h, n = 53; ICU stay < 48 h, n = 33), 205 patients were excluded and 256 were enrolled, of whom 255 formed the final analysis cohort. In the external cohort, 5940 ICU patients with TBI aged ≥ 18 years were identified from the MIMIC-IV database; after applying the exclusion criteria (pre-existing renal disease, n = 925; congestive heart failure or previous cardiac surgery, n = 1359; history of malignancy, n = 599; history of

craniocerebral surgery, n = 47; multiple ICU admissions, n = 1175; no relevant renal measurements within 24 h, n = 137; ICU stay < 48 h, n = 231; ICU type other than NSICU, n = 1347), 5820 patients were excluded and 120 were finally included. The enrolled patients of the local cohort were randomly split into a training set (70%) for model development and an internal validation set (30%). The AKI incidence was 47.1% (120/255) in the local cohort and 24.2% (29/120) in the external cohort, and this difference was statistically significant ($\chi^2 = 16.91$, $P < 0.001$), indicating a shift in population composition.

Baseline characteristics of the local cohort stratified by AKI status are shown in Table 1. Severe TBI (GCS ≤ 8), total SOFA score, first-day fluid balance, use of loop diuretics and mannitol, vasoactive drugs, magnesium, CK-MB, creatinine, sex, and pupillary abnormality differed significantly between the two groups (all $P < 0.05$). The standardised mean differences for each variable between the AKI and non-AKI groups are presented in Supplementary Figure S2.

Table 1
Baseline characteristics of the local development cohort stratified by AKI

Variable	Type	Non-AKI (n = 135)	AKI (n = 120)	Test	P value
Sex (M/F)	Categorical	85/50	95/25	χ^2	0.007
Age (years)	Continuous	64.00[55.00–70.00]	63.00[55.00–74.00]	MWU	0.293
BMI (kg/m²)	Continuous	23.80 ± 2.36	24.02 ± 2.16	t	0.441
Hypertension (No/Yes)	Categorical	79/56	75/45	χ^2	0.603
Diabetes mellitus (No/Yes)	Categorical	119/16	99/21	χ^2	0.271
Emergency hypoxia (No/Yes)	Categorical	125/10	113/7	χ^2	0.801
Emergency shock (No/Yes)	Categorical	128/7	115/5	χ^2	0.931
Emergency intubation (No/Yes)	Categorical	95/40	77/43	χ^2	0.357
Pupillary abnormality	Categorical	60/64/11	54/42/24	χ^2	0.012
Rotterdam CT score	Continuous	4.00[3.00–5.00]	4.00[4.00–5.00]	MWU	0.077
ISS (sum of squares of AIS)	Continuous	23.05 ± 8.40	24.00[21.00–29.00]	MWU	0.155
Total SOFA score	Continuous	4.00[3.00–7.00]	6.00[4.00–8.00]	MWU	< 0.001
TBI grade (1/2/3)	Categorical	12/26/97	2/7/111	χ^2	< 0.001
Systolic blood pressure (SBP) (mmHg)	Continuous	136.67 ± 24.59	139.86 ± 26.13	t	0.318
Mean arterial pressure, MAP (mmHg)	Continuous	98.09 ± 16.33	101.11 ± 16.87	t	0.149
First-day fluid balance (mL)	Continuous	352.50[0.00–927.50]	35.53[− 479.15–708.73]	MWU	0.004
Loop diuretics within 48 h (No/Yes)	Categorical	121/14	87/33	χ^2	0.001
Mannitol (within 48 h) (No/Yes)	Categorical	13/122	23/97	χ^2	0.045
Vasoactive drugs (No/Yes)	Categorical	119/16	90/30	χ^2	0.010

Variable	Type	Non-AKI (n = 135)	AKI (n = 120)	Test	P value
Mechanical ventilation (No/Yes)	Categorical	103/32	79/41	χ^2	0.088
Surgery (No/Yes)	Categorical	69/66	72/48	χ^2	0.099
In-hospital blood transfusion (No/Yes)	Categorical	63/72	44/76	χ^2	0.137
Magnesium, admission (mmol/L)	Continuous	0.80 ± 0.08	0.78 ± 0.08	t	0.013
CK-MB (ng/mL)	Continuous	3.20[1.40–5.36]	4.16[1.98–6.27]	MWU	0.027
Creatinine (μmol/L)	Continuous	58.94 ± 14.07	63.56 ± 16.49	t	0.018
Urea (mmol/L)	Continuous	5.98 ± 1.67	6.22 ± 1.66	t	0.244

Continuous variables are shown as mean ± SD (compared by Student's t-test) or median [IQR] (Mann–Whitney U test), and categorical variables as counts (chi-square test). χ^2, chi-square test; MWU, Mann–Whitney U test; t, Student's t-test. Pupillary abnormality: coded from admission pupil status as bilaterally equal = 0, unequal (anisocoria) = 1, bilaterally fixed/dilated = 2, and unrecordable = 3; the table presents a grouped 3-level display in which level 2 combines bilaterally fixed/dilated (code 2) and unrecordable (code 3). Unrecordable pupils (code 3; 16/255 locally, 9/120 externally) were included as abnormal in the primary analysis.

Note

For continuous variables conforming to a normal distribution, data are presented as mean ± standard deviation and compared using Welch's t-test; the remaining variables are presented as median (P25–P75) and compared using the Mann–Whitney U test. Categorical variables are presented as frequencies and proportions and compared using the χ^2 test (with Yates' correction or Fisher's exact test when the expected frequency was < 5). AKI group: n = 120; non-AKI group: n = 135. The missingness rate for each variable in the local cohort was < 5%.

3.2 Risk-factor screening (local cohort)

The results of univariable and multivariable logistic regression are summarised in Table 2. Multivariable analysis showed that severe TBI (GCS ≤ 8), loop-diuretic use within 48 h and elevated CK-MB were positively associated with AKI (independently associated), whereas greater first-day fluid balance and mannitol use within 48 h were inversely associated (all $P < 0.05$). Neither the 72-h magnesium nadir nor pupillary abnormality reached statistical significance. These associations are presented graphically as a forest plot in Fig. 2. The distribution of the 72-h magnesium nadir between the AKI and non-AKI groups is shown in Supplementary Figure S3. Treating unrecordable pupils as missing rather than abnormal (16/255 locally and 9/120 externally) yielded essentially unchanged estimates: the adjusted OR for

pupillary abnormality changed only from 0.69 (primary analysis, unrecordable coded as abnormal) to 0.67 (sensitivity analysis, coded as missing), indicating that this finding was insensitive to the coding choice.

Table 2
Multivariable logistic regression of AKI risk factors in the local TBI cohort (n = 249).

Variable	Univariable crude OR (95% CI)	P	Multivariable aOR (95% CI)	P
Severe TBI (GCS ≤ 8)	4.832 (2.224–10.498)	< 0.001	9.417 (3.743–23.694)	< 0.001
Loop-diuretic use within 48 h	3.278 (1.656–6.491)	0.001	3.925 (1.736–8.874)	0.001
CK-MB (per 1 SD)	1.298 (1.010–1.668)	0.042	1.785 (1.301–2.447)	< 0.001
First-day fluid balance (per 1 SD)	0.692 (0.536–0.894)	0.005	0.600 (0.442–0.814)	0.001
Mannitol use within 48 h	0.449 (0.216–0.933)	0.032	0.372 (0.159–0.868)	0.022
72-h magnesium nadir (per 1 SD)	0.718 (0.554–0.931)	0.013	0.762 (0.565–1.028)	0.075
Pupillary abnormality (any)	0.978 (0.596–1.603)	0.929	0.687 (0.375–1.259)	0.224

Note: Odds ratios for continuous variables are reported per 1-SD increase, and categorical variables as present versus absent. aOR = adjusted odds ratio. Estimates were derived from 249 complete cases (listwise deletion across the seven predictors) of the local cohort (n = 255). SDs used for standardisation in the local cohort were 2.82 ng/mL for CK-MB, 0.092 mmol/L for the 72-h magnesium nadir and 680 mL for first-day fluid balance; equivalently, per 1 ng/mL CK-MB the odds ratio was 1.23 (95% CI 1.10–1.37), per 0.1 mmol/L increase in the 72-h magnesium nadir it was 0.75 (95% CI 0.54–1.03), and per 500 mL increase in first-day fluid balance it was 0.69 (95% CI 0.55–0.86).

3.3 External cohort validation

The same association analysis was repeated in the external MIMIC-IV cohort (n = 120; 29 AKI cases) using the same variables and coding wherever available. As shown in Table 3, none of the candidate factors reached statistical significance in univariable analysis in the external cohort (all P > 0.05). The conventional external multivariable model could not be stably estimated because of the small number of events (n = 29); we therefore fitted a Firth-penalised logistic regression (six predictors; CK-MB excluded), and all six predictors remained non-significant (see Supplementary Table S4). The AKI incidence in the external cohort (24.2%) was significantly lower than that in the local cohort (47.1%, P < 0.001), and there were marked inter-centre differences in median first-day fluid balance (approximately 1150 mL in the external cohort versus 211 mL locally) and in CK-MB availability (92.5% missing). The external cohort was also considerably less severely injured than the local cohort, with severe TBI (GCS ≤ 8) present in only 10.0% (12/120) versus 81.6% (208/255) locally. Some of this contrast may reflect differences in

GCS documentation between the databases (see Methods), and these differences, together with the fact that urine-output data were largely incomplete in MIMIC-IV, suggest that the failure to externally validate the risk-factor associations was mainly attributable to distribution shifts in population composition and clinical practice rather than evidence that the associations do not exist; the external results should therefore be interpreted as hypothesis-generating. The external cohort is derived from a single US academic medical centre (Beth Israel Deaconess Medical Center), so this “external” comparison contrasts our centre against one institution rather than a multi-centre population. The magnitude of inter-centre imbalance is quantified in Supplementary Figure S4 (standardised mean differences between cohorts) and Supplementary Table S3 (external-cohort baseline characteristics; no surgical procedures were captured in the extracted MIMIC-IV records).

Table 3
Validation of risk-factor associations in the external MIMIC-IV cohort (n = 120)

Variable	Univariable crude OR (95% CI)	P	Multivariable aOR (95% CI)	P
Severe TBI (GCS ≤ 8)	1.051 (0.265–4.175)	0.943	—	—
Loop-diuretic use within 48 h	2.161 (0.647–7.221)	0.210	—	—
CK-MB (per 1 SD)	Missing > 90%, not evaluable	—	—	—
First-day fluid balance (per 1 SD)	1.100 (0.730–1.656)	0.649	—	—
Mannitol use within 48 h	0.325 (0.039–2.684)	0.297	—	—
72-h magnesium nadir (per 1 SD)	1.053 (0.692–1.602)	0.808	—	—
Pupillary abnormality (any)	0.606 (0.188–1.954)	0.402	—	—

Note: CK-MB was missing in 111 of 120 cases (92.5%) in the external cohort and was therefore excluded from the external analysis. Owing to the small number of events (n = 29), the external multivariable model could not be stably estimated by ordinary logistic regression; a Firth-penalised logistic regression (six predictors; CK-MB excluded) was therefore fitted and is reported in Supplementary Table S4, where all six predictors remained non-significant.

Discussion

This study identified multiple independent correlates of AKI in a single-centre TBI cohort: severe TBI (GCS ≤ 8), loop-diuretic use within 48 h and elevated CK-MB were positively associated with AKI, whereas early fluid-management variables (first-day fluid balance and mannitol use) were inversely associated. The strong association between severe TBI and AKI (aOR 9.42) is consistent with systemic stress, sympathetic activation and rhabdomyolysis (muscle injury) leading to impaired renal perfusion; elevated CK-MB, separately, reflects myocardial injury, suggesting that cardiorenal syndrome may contribute to

AKI following TBI [9]; and loop-diuretic use, as a positive correlate of AKI, may reflect greater illness severity or more complex volume management [10]. Notably, first-day fluid balance and mannitol use showed inverse associations in this model, a direction that is inconsistent with some previous reports [11–13]; this most likely reflects indication bias (patients with milder disease who received more active dehydrating therapy were more likely to be treated) rather than evidence that fluid management itself reduces the risk of kidney injury, and should be interpreted with caution pending confirmation in a prospective study. The 72-h magnesium nadir was not independently associated with AKI in our cohort, although both hypomagnesaemia and magnesium derangement have been linked to adverse renal outcomes in critically ill patients [14, 15]; this null finding should be interpreted in light of the narrow range of magnesium values observed.

A further key finding of this study is that none of the candidate risk factors reached significance in the external MIMIC-IV cohort, in which a multivariable model could not be estimated by conventional logistic regression because of the small number of events (n = 29, EPV ≈ 4); the prediction model likewise showed no external discrimination (AUC 0.531). The AKI incidence in the external cohort (24.2%) was much lower than that in the local cohort (47.1%), and there were marked inter-centre differences in fluid balance, CK-MB availability and other variables. These differences are attributable at least as much to cross-centre measurement heterogeneity as to genuine variation in underlying risk. In MIMIC-IV, urine-output data were largely incomplete, under-ascertaining AKI defined by the KDIGO urine-output criterion and depressing the external AKI incidence; moreover, GCS was frequently recorded under sedation, attenuating the severe-TBI signal that dominated locally. Together with the limited number of events (n = 29, EPV ≈ 4), these measurement incompatibilities—rather than centre-specific biology alone—best explain the failure of external validation, indicating that single-centre models cannot be readily extrapolated. Acknowledging this is more honest than claiming to have developed a generalisable prediction model, and it indicates the direction for future multicentre studies. Interestingly, a simple generic SOFA score (assessed post hoc as an exploratory benchmark) achieved better external discrimination (AUC 0.656) than any of the locally developed TBI-specific models (multivariable logistic regression 0.531, random forest 0.554, XGBoost 0.517; Supplementary Table S1). This indicates that a readily available organ-failure score transports across centres better than models built on centre-specific risk factors, and further highlights the limited generalisability of single-centre prediction tools.

Contextualising these results with previous TBI and AKI literature clarifies the contribution of this study. Wankhade et al. [2] reported a single-centre retrospective TBI and AKI cohort and likewise implicated injury severity and diuretic exposure, but that study did not attempt external validation. The present work deliberately tested reproducibility in an independent MIMIC-IV population and transparently reports its failure to validate externally, which positions the findings as hypothesis-generating rather than as a claim of a generalisable model. Barea-Mendoza et al. [3], using multicentre data, identified several AKI risk factors and emphasised centre dependence; our single-centre results are consistent with this view while adding finer resolution on early fluid-balance and mannitol effects that large registries seldom model at this level. We additionally examined the 72-h magnesium nadir, an electrolyte disturbance rarely studied in TBI; although null here, its prognostic links to AKI reported elsewhere [14, 15] warrant prospective

evaluation. Our local AKI incidence (47.1%) exceeds the 20–30% typical of TBI cohorts that relied predominantly on creatinine-based definitions [3]; we attribute this to the combined creatinine and urine-output KDIGO criteria applied in our neurosurgical ICU and to a more severely injured case-mix (note that the external MIMIC cohort was considerably less severely injured, with severe TBI (GCS ≤ 8) present in only 10.0% (12/120) versus 81.6% (208/255) locally), whereas the external MIMIC cohort (24.2%) aligns with that 20–30% range because urine-output data were largely incomplete; the exact proportion of AKI attributable to the urine-output criterion alone could not be quantified because urine-output records were not exported to the analysis dataset.

This study has several limitations. (1) The single-centre retrospective design is susceptible to selection bias and unmeasured confounding, so causal inferences must be drawn with caution. (2) In the external validation cohort, CK-MB was missing in as many as 92.5% of cases, limiting assessment of myocardial injury markers in the external validation, and only 29 events were available (EPV ≈ 4), giving insufficient statistical power; the external results are therefore interpreted only as hypothesis-generating and cannot be taken as evidence that the associations do not exist. (3) Mortality and other prognostic follow-up data were unavailable, so no survival or prognostic analysis was performed. (4) The prediction model was developed in a single centre and internally validated in a small sample, and its extrapolability is limited; it has not been validated in a prospective multicentre population. (5) Because AKI was defined as occurring at any time during hospitalisation while several predictors were measured within the first 48–72 h, for patients developing AKI very early the temporal ordering between some predictors and AKI onset cannot be strictly guaranteed, limiting causal interpretation; a landmark sensitivity analysis (restricting AKI to events occurring after the predictor-measurement window) was therefore not possible, because the dataset was an aggregated analytic extract in which individual measurement timestamps were not retained and the exact time of AKI onset could not be reconstructed. (6) The external validation was against a single foreign academic centre, limiting generalisability claims. (7) Because CK-MB was unavailable in > 90% of the external cohort, future external validation should employ creatine kinase or cardiac troponin, which more directly reflect muscle and myocardial injury. (8) The external validation cohort was considerably less severely injured than the local cohort, with severe TBI (GCS ≤ 8) present in only 10.0% (12/120) versus 81.6% (208/255) locally, which may further explain its lower AKI incidence and the limited external transportability of the risk factors.

With respect to generalisability, these results are mainly applicable to NSICU populations in regional teaching hospitals with similar spectra of trauma and levels of intensive care; differences in injury mechanisms, volume management and baseline renal-injury risk across ICUs of different levels and regions may affect the direction and strength of each risk factor and should therefore be considered when extrapolating these conclusions.

Conclusions

In the local cohort, AKI following TBI is influenced by multiple factors, including severe TBI, loop-diuretic use and myocardial injury markers, with several early fluid-management factors showing inverse

associations. The inverse associations with first-day fluid balance and mannitol should not be interpreted causally, as they most likely reflect indication bias (patients with milder disease who received more active dehydrating therapy) rather than a renoprotective effect of fluid management. However, neither the risk-factor associations nor the prediction model generalised to the external cohort, suggesting centre specificity. We recommend that future multicentre, prospective studies be conducted to validate and refine risk-stratification tools for AKI after TBI.

Abbreviations

AIS
Abbreviated Injury Scale
AKI
acute kidney injury
aOR
adjusted odds ratio
AUC
area under the receiver operating characteristic curve
CI
confidence interval
CK-MB
creatine kinase myocardial band
EPV
events per variable
GCS
Glasgow Coma Scale
HIS
hospital information system
ICU
intensive care unit
ISS
Injury Severity Score
KDIGO
Kidney Disease:Improving Global Outcomes
MDRD
Modification of Diet in Renal Disease
MIMIC-IV
Medical Information Mart for Intensive Care IV
MLR
multivariable logistic regression
NSICU

neurosurgical intensive care unit
OR
odds ratio
RF
random forest
Rotterdam CT score
computed tomography-based severity score for traumatic brain injury
SCr
serum creatinine
SD
standard deviation
SMD
standardised mean difference
SOFA
Sequential Organ Failure Assessment
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
TBI
traumatic brain injury
TRIPOD
Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Affiliated Hospital of Nantong University (approval number: 2025-K280). Because the study was retrospective and the data were de-identified, informed consent was waived. Use of the MIMIC-IV database was certified through the PhysioNet/National Institutes of Health CITI programme (certification ID: CR-67347346) and complied with its data-use agreement; release of MIMIC-IV was approved by the Beth Israel Deaconess Medical Center Institutional Review Board, with waiver of informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Conceptualization: JLS; Data curation: JKZ; Formal analysis: CHL,JKZ, MJL; Investigation: JKZ; Methodology: CHL; Software: CHL; Supervision: JLS, JMS; Writing – original draft: CHL, JKZ, MJL; Writing – review and editing:JMS. All authors read and approved the final manuscript.

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Not applicable.

Availability of data and materials

The de-identified data of the local cohort will not be made publicly available owing to ethical and privacy restrictions; researchers may request reasonable access from the corresponding author (subject to approval by the ethics committee). MIMIC-IV data were obtained from the PhysioNet platform under its data use agreement (https://physionet.org/content/mimiciv/).

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Figures

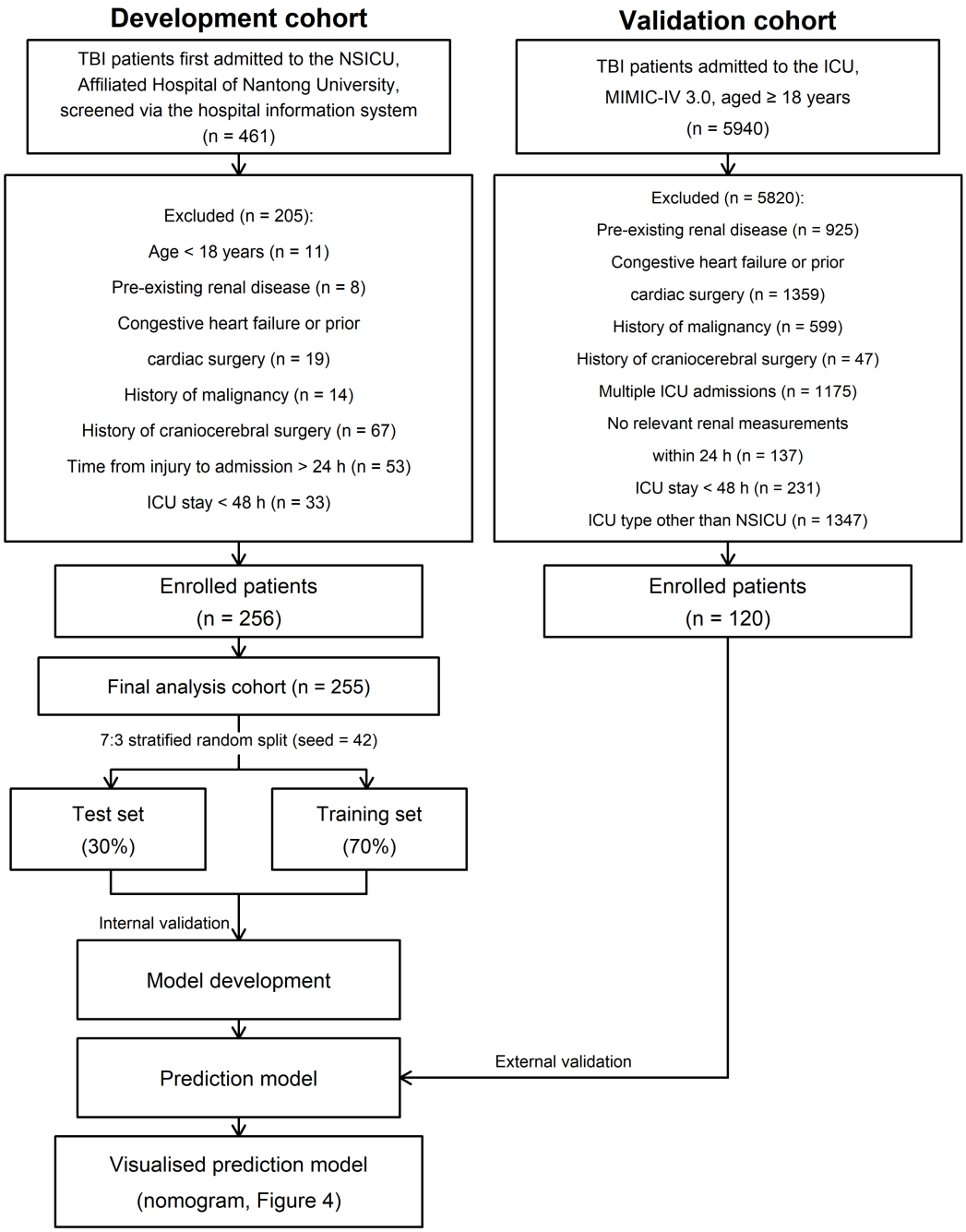


Figure 1

Flow chart of participant screening, exclusion, cohort construction and model development. Patients in the development cohort were admitted to the NSICU of the Affiliated Hospital of Nantong University; patients in the validation cohort were identified from the MIMIC-IV database. TBI = traumatic brain injury; NSICU = neurosurgical intensive care unit; HIS = hospital information system; MIMIC-IV = Medical Information Mart for Intensive Care IV.

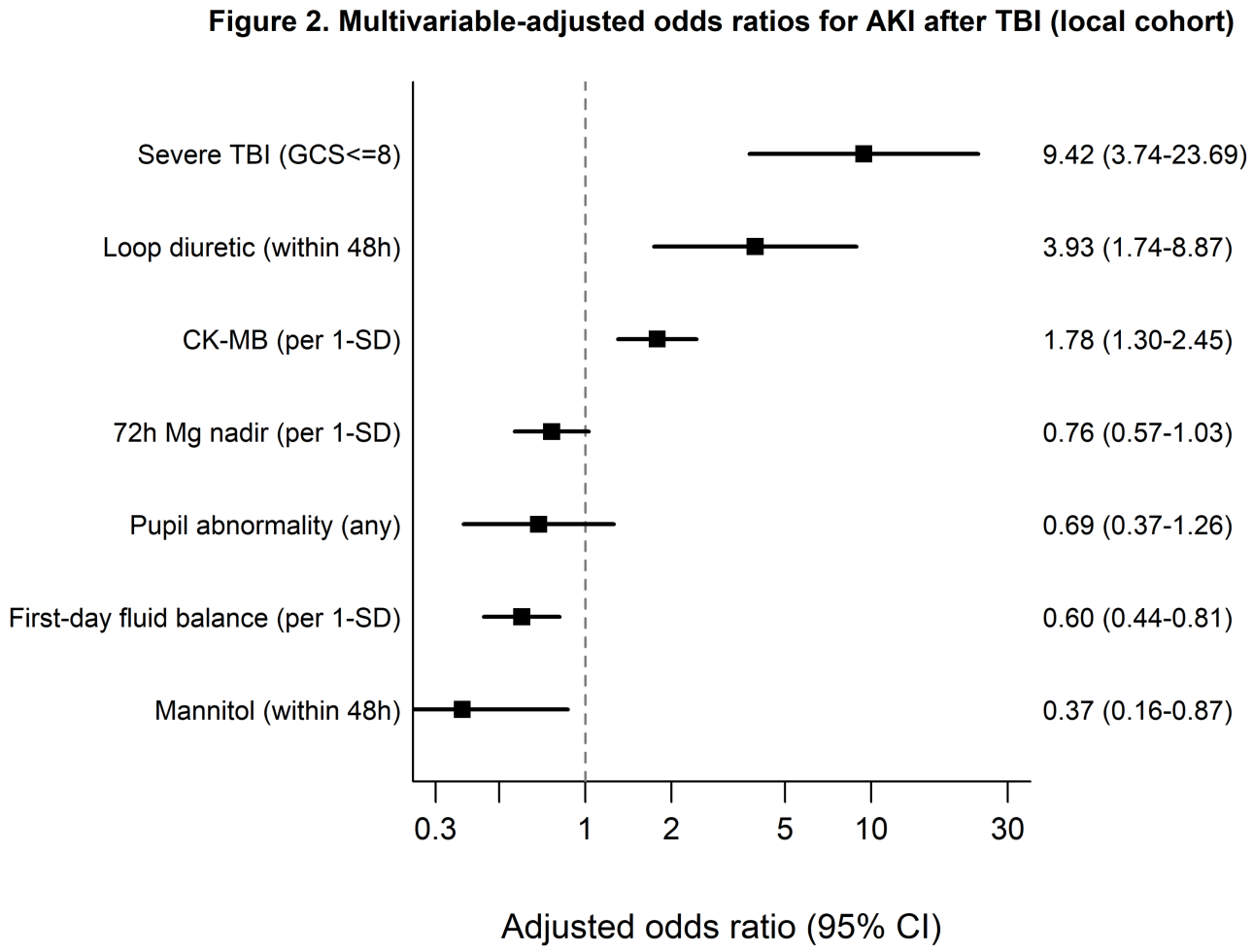


Figure 2

Forest plot of AKI risk-factor associations in the local TBI cohort (n = 249). Squares indicate odds ratios and horizontal lines indicate 95% confidence intervals; the vertical reference line indicates an odds ratio of 1.0.

Supplementary Files

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