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Predictive value of triglyceride glucose index in acute kidney injury in patients with severe traumatic brain injury

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Background At present, the relationship between the Triglyceride-glucose index (TyG index) and Acute kidney injury (AKI) in traumatic brain injury patients in the Intensive Care Unit (ICU) is still unclear. Currently, the relationship between TyG index and AKI occurred within 7 days in the ICU is a highly researched and trending topic. **Objective** In this study, we conducted in-depth exploration of the relationship between the development of AKI in traumatic brain injury (TBI) patients in the ICU and changes in TyG index, as well as its relevance. **Methods** A cross-sectional study was conducted with a total of 492 individuals enrolled in the Medical Information Mart for Intensive Care IV(MIMIC-IV) database. Multivariate model logistic regression, smoothed curve fitting and forest plots were utilized to confirm the study objectives. The predictive power of the TyG index for outcome indicators was assessed using subject work characteristics (ROC) curves. As well as comparing the Integrated Discriminant Improvement Index and the Net Reclassification Index of the traditional forecasting model with the addition of the TyG index. **Results** Of all eligible subjects, 55.9% were male and the incidence of AKI was 59.3%. There was a statistically significant difference in the incidence of AKI within 7 days in the ICU between the different TyG index groups. The difference between TyG index and the risk of AKI within 7 days in the ICU remained significant after adjustment for logistic multifactorial modeling (OR = 2.07, 95% CI = 1.41–3.05, $P < 0.001$). A similar pattern of associations was observed in subgroup analyses (P values for all interactions were greater than 0.05). The addition of TyG index to the traditional risk factor model improved the predictive power of the risk of AKI within 7 days in ICU ($P < 0.05$). **Conclusion** The findings of this study demonstrate a strong association between the TyG index and the occurrence of AKI within 7 days in ICU patients. The TyG index can potentially be used as a risk stratification tool for early identification and prevention of AKI. Implementing preventive strategies targeting patients with a high TyG index may help reduce the burden of AKI in the ICU. Further prospective studies are warranted to validate these findings and explore the clinical utility of the TyG index in AKI prevention.

Keywords Acute kidney injury, Triglyceride glucose index, Intensive care unit, Prevention strategies, MIMIC-IV database

Background

TBI has the highest prevalence of all common neurological disorders and poses a significant public health burden. It is estimated that TBI will remain one of the top three causes of injury-related death and disability through 2030. Overall, 50–60 million people suffer from TBI each year, costing the global economy an estimated $400 billion annually[1]. TBI is a leading cause of death and persistent neurocognitive impairment in adults and can lead to a variety of non-neurologic complications, including AKI[2]. According to published studies, the incidence of AKI in patients with TBI ranges from 3.9–24%[3,4]. Notably, the pathophysiologic effects of

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secondary brain injury can exacerbate the development of AKI after TBI[5]. Therefore, as neurosurgeons and ICU physicians, it is more important to pay attention to the occurrence and development of AKI in early stage patients and to reduce the number of drugs with high renal impairment[6]. In particular, the use of mannitol analogs should be reduced and the use of hypertonic saline should be increased in the treatment of intracranial pressure reduction[7]. As the global population ages, the burden of TBI patients in ICU is increasing. Therefore, it is crucial to identify indicators that can predict the occurrence of AKI in patients with TBI. These indicators should be straightforward, user-friendly, cost-effective, and easy to apply in a clinical setting.

Factors that can predict the occurrence of AKI in critically ill TBI patients are crucial. TyG index is a recognized indirect marker of insulin resistance (IR), combining fasting blood glucose (FBG) and triglyceride (TG) levels[8–10]. It has been widely used to assess the relationship between lipid metabolism and glycemic status and has been shown to be effective in predicting adverse cardiovascular disease outcomes[11–16]. Although the prognostic efficacy of TyG index in predicting the prediction of complications, recurrence, morbidity, and mortality in patients with other brain disorders and in other diseases has been demonstrated[17–24].The role of TyG index in predicting the occurrence of AKI in patients with TBI, especially in critically ill patients, is unknown.

Therefore, the aim of this study was to test whether the TyG index can be used as a predictor of the occurrence of AKI in patients with TBI in the ICU. This may help to differentiate patients at higher risk for closer monitoring or early intervention.

Method

Data selection

This was a cross-sectional study, and the original data were obtained from the MIMIC-IV database. The MIMIC-IV database is a joint venture between the MIT Laboratory of Computational Physiology, the Beth Israel Deaconess Medical Center (BIDMC) at Harvard Medical School, and Philips Healthcare. With funding from the National Institutes of Health, the database was launched in 2003[25].

In order to comply with the regulations, the author, Huang Jiang, obtained both a Cooperative Institutional Training Initiative (CITI) license and the necessary permissions to use the MIMIC-IV database (ID: 12801436).

Inclusion criteria: Diagnosis of TBI (based on International Classification of Diseases, Ninth Edition (ICD-9) or International Classification of Diseases, Tenth Edition (ICD-10)). Exclusion criteria: (a) lack of admission to the ICU and (b) lack of triglyceride and blood glucose data. For patients with multiple admissions to the ICU, we chose the first admission. To ensure data completeness, we excluded patients with no AKI data, incomplete TG or glucose levels, or no follow-up 48 h after admission. Patients were divided into three groups according to the tertiles of the TyG index on day 1 in the ICU. For patients with multiple tests, the first test result within 24 h of ICU admission was used.

Data collection

Data collection consisted of extracting patient demographic characteristics, laboratory indicators, comorbidities, first day in and out of ICU, in-hospital mortality, and scores using the Structured Query Language (SQL) of PostgreSQL (version 16). Demographic information includes gender, age and race. Vital signs included heart rate, oxygen saturation (Spo2), systolic blood pressure (SBP) mean blood pressure (MBP). Laboratory indices included Red Blood Cell Distribution Width (RDW), blood urea nitrogen (BUN), white blood cell count (WBC), prothrombin time (PTT), creatinine, hemoglobin, blood calcium, blood glucose, blood sodium and blood potassium. Patient comorbidities and personal history were determined based on ICD-9 and ICD-10 and included AKI, sepsis, myocardial infarction, congestive heart failure, chronic lung disease, diabetes mellitus, renal disease, and Charlson Comorbidity Index. Scores included The Glasgow Coma Scale (GCS), Acute Physiology Score III (APSIII), Oxford Acute Severity Score (OASIS), Sequential Organ Failure Score (SOFA), and Simplified Acute Physiology Score (SAPSII).

The TyG index was calculated as follows: $\ln[(\text{fasting TG (mg/dl)} \times \text{FBG (mg/dl)})/2]$. The diagnostic criteria for sepsis 3.0 are as follows: infection and SOFA score of ≥ 2. For variables with a percentage of missing values greater than 25%, we directly deleted them; for variables with a percentage of missing values less than 25%, we used multiple interpolation(based on 5 replications and a chained equation approach method) to interpolate the missing values. For data before and after multiple interpolation, we performed a baseline profile comparison (Supplementary Table 1). Body mass index (BMI), glutamate aminotransferase, C-reactive protein, uric acid, and cystatin C all had missing values greater than 25%.

Outcome measures

The risk of acute kidney failure was the primary outcome of this study. According to the Kidney Disease: Improving Global Outcomes (KDIGO)[26]guidelines, AKI is defined as a serum creatinine (SCr) level ≥ 0.3 mg/dL above baseline within 48 h or a urine output of < 0.5 mL/kg/h within 6 h.

Statistical analysis

Categorical data are presented as frequencies and percentages (%), and continuous data are presented as mean (standard deviation (SD)) or median (interquartile spacing). Differences in continuous variables were tested using analysis of variance (ANOVA) or rank sum tests. We used the maximum Yoden index to determine the best cut-off value for both and grouped the TyG index according to the best cut-off value. To compare the characteristics of subjects in the outcome group, the chi-square test or Fisher's exact test was used for categorical variables. Multivariate logistic regression analyses were used to assess the independent correlation between TyG index and the risk of developing AKI in patients with traumatic brain injury. TyG index was entered as a categorical variable (trichotomous) and as a continuous variable (with odds ratios (ORs) calculated for each incremental unit). Regression analyses using three models. The multivariate models were adjusted as follows:

Model 1 was unadjusted; Model 2 was adjusted for age, sex and race; Model 3 was adjusted to Model 2 for GCS, apsiii, sapsii, oasis, sofa24, sepsis3, chronic pulmonary disease, myocardial infarct, renal disease, congestive heart failure, diabetes, input1day and RDW. To prevent multicollinearity, variables with variance inflation factors greater than 5 were excluded from the model (Supplementary Table 2). A restricted cubic spline model was used to explore the possible linear relationship between TyG index and AKI. The lowest tertile of TyG index values was used as the analytical reference group to adjust for the above (Model 3) covariates. The tertile level was used as an ordinal variable to derive a p-value for trend. To further assess the effect of unmeasured confounders, we calculated the E-value.

Clinical decision curves and calibration plots (Supplementary Fig. 1) were plotted, and Integrated Discriminant Improvement (IDI)[27] and Net Reclassification Index (NRI) were calculated separately to assess the improvement in predictive power and clinical value of the scoring tool by incorporating the TyG index. We further stratified analyses by age, sex, race, and sepsis and diabetes to determine the robustness of the TyG index in predicting AKI risk. To test the interaction between the TyG index and the stratification variables, we used the likelihood ratio test. To reduce the risk of category I errors (false positives), Least Significant Difference (LSD) and Bonferroni were performed to compare TyG index between groups in the event of AKI (Supplementary Table 3). A two tailed test was used in this study, and $P < 0.05$ was considered a statistically significant difference. All analyses were performed using the R Statistical Package (http://www.R-project.org, R Foundation) and Free Statistical Software version 1.9.1.

Ethics approval and consent to participate

The MIMIC-IV project was approved by the Institutional Review Boards of the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Centre. Patient information was anonymised and informed consent was not required for this study. The ethical approval and participation consent followed the Helsinki Declaration guidelines.

Result

A total of 492 patients were finally included in this study. The patient selection process is shown in Fig. 1. AKI was diagnosed in 292 patients (59.3%).The mean age of the patients was (68.9 ± 15.9) years and 275 patients (55.9%) were male. The mean TyG index of all subjects was (8.9 ± 0.7).

Study population characteristics

We determined the optimal cut-off value for both by maximising the Jordon's index, where the sensitivity (66.8%) and specificity (63.5%) of the TyG index in predicting the occurrence of AKI reached its maximum value at 8.7052 points. We then changed the TyG index into a triple categorical variable based on the optimal cut-off value(three groups - Q1: 7.30–8.51; Q2: 8.51–9.05; and Q3: 9.05–12.10). Patients in the high TyG index group had elevated levels of sepsis, diabetes, GCS, apsiii score, sofa score, oasis score, BUN, WBC, and heart rate compared to the low TyG index group. The incidence of AKI (42.7% vs. 60.4% vs. 75%, $P < 0.001$) increased progressively with increasing TyG index (Table 1).

Univariate logistic regression analysis of the incidence rate of AKI

TyG index was a risk factor for AKI (Table 2). However, univariate analysis also showed that gender, age, ethnicity, BUN, calcium, LDH, heart rate, MBP, WBC, PTT, glucose, hemoglobin, sepsis, myocardial infarction, congestive heart failure, chronic pulmonary disease, Diabetes, GCS, apsiii score, sapsii score and Oasis score were the correlates of AKI ($P < 0.05$).

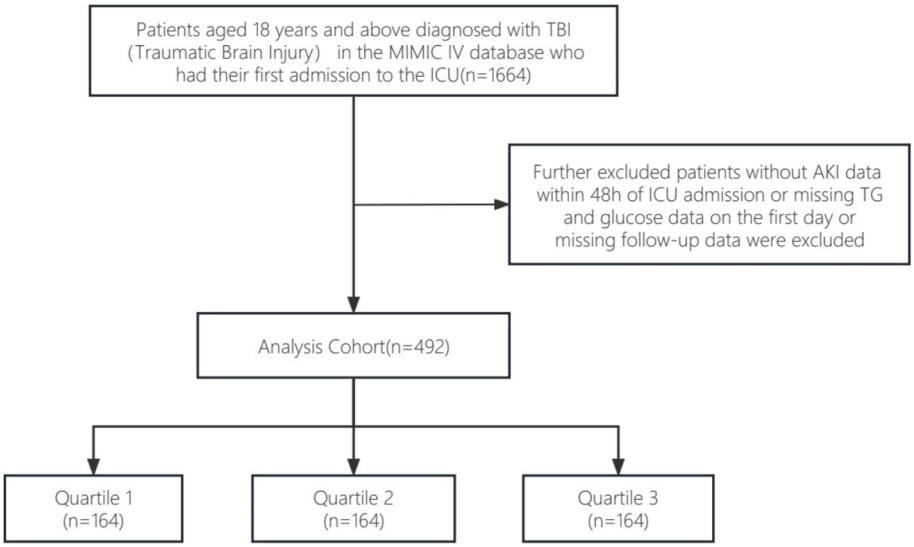

Figure 1. Flowchart of patient selection.

Variables	Total ($n=492$)	Q1 ($n=164$) (7.30–8.51)	Q2 ($n=164$) (8.51–9.05)	Q3 ($n=164$) (9.05–12.10)	*P*
Race = white, n (%)	281 (57.1)	103 (62.8)	100 (61)	78 (47.6)	0.01
Gender = male, n (%)	275 (55.9)	79 (48.2)	96 (58.5)	100 (61)	0.046
Age, mean ± sd	68.9 ± 15.9	71.1 ± 16.6	70.4 ± 14.6	65.1 ± 15.7	< 0.001
Aki, n (%)	292 (59.3)	70 (42.7)	99 (60.4)	123 (75)	< 0.001
Sepsis3, n (%)	196 (39.8)	50 (30.5)	59 (36)	87 (53)	< 0.001
Myocardial infarct, n (%)	53 (10.8)	11 (6.7)	18 (11)	24 (14.6)	0.068
Congestive heart failure, n (%)	62 (12.6)	18 (11)	22 (13.4)	22 (13.4)	0.744
Chronic pulmonary disease, n (%)	50 (10.2)	11 (6.7)	16 (9.8)	23 (14)	0.088
Diabetes, n (%)	129 (26.2)	24 (14.6)	38 (23.2)	67 (40.9)	< 0.001
dementia, n (%)	50 (10.2)	25 (15.2)	17 (10.4)	8 (4.9)	0.008
Renal disease, n (%)	64 (13.0)	16 (9.8)	19 (11.6)	29 (17.7)	0.082
Charlson comorbidity index, mean ± sd	6.4 ± 2.7	6.3 ± 2.4	6.4 ± 2.5	6.4 ± 3.1	0.971
GCS, mean ± sd	11.0 ± 3.6	11.8 ± 3.1	11.3 ± 3.4	9.9 ± 3.9	< 0.001
Apsiii, mean ± sd	43.4 ± 20.9	38.6 ± 17.4	40.3 ± 18.3	51.4 ± 24.1	< 0.001
Sapsii, mean ± sd	33.1 ± 10.5	32.6 ± 10.8	32.2 ± 9.6	34.5 ± 10.8	0.113
Oasis, mean ± sd	33.1 ± 8.3	31.2 ± 7.9	33.1 ± 7.8	35.1 ± 8.7	< 0.001
Sofa24, mean ± sd	3.3 ± 2.7	2.8 ± 2.3	2.9 ± 2.3	4.2 ± 3.1	< 0.001
Calcium, mean ± sd	8.9 ± 0.7	9.0 ± 0.6	9.0 ± 0.6	8.8 ± 0.8	0.076
Heart rate, mean ± sd	80.2 ± 14.0	77.6 ± 13.9	80.9 ± 12.2	82.0 ± 15.4	0.014
Sbp, mean ± sd	102.3 ± 15.9	102.3 ± 16.6	104.3 ± 14.8	100.3 ± 16.2	0.076
Mbp, mean ± sd	66.6 ± 13.6	67.8 ± 13.2	67.8 ± 12.6	64.3 ± 14.8	0.026
Spo2, mean ± sd	92.1 ± 6.4	92.1 ± 4.6	92.5 ± 4.9	91.9 ± 8.9	0.714
input1day, median (iqr)	2104.4 (1352.5, 3127.7)	1996.3 (1193.8, 2479.6)	2000.0 (1283.9, 2973.5)	2655.5 (1820.1, 4267.0)	< 0.001
output1day, median (iqr)	1662.0 (1063.0, 2307.2)	1504.0 (865.0, 2225.0)	1697.5 (1121.0, 2321.2)	1796.0 (1210.5, 2363.5)	0.027
RDW, mean ± sd	13.5 ± 3.2	13.4 ± 3.1	13.3 ± 3.6	13.7 ± 2.6	0.517
Wbc, median (iqr)	9.9 (7.7, 13.5)	8.6 (7.1, 10.9)	10.4 (8.2, 13.3)	12.0 (8.1, 14.9)	< 0.001
Glucose, median (iqr)	133.0 (110.0, 165.2)	115.0 (99.0, 137.5)	130.0 (114.0, 151.0)	155.5 (129.8, 208.2)	< 0.001
Potassium, mean ± sd	3.8 ± 0.5	3.8 ± 0.5	3.8 ± 0.5	3.8 ± 0.6	0.654
Sodium, mean ± sd	141.6 ± 4.8	141.3 ± 4.2	141.5 ± 4.9	141.8 ± 5.4	0.644
hemoglobin, mean ± SD	11.5 ± 2.1	11.6 ± 2.0	11.7 ± 2.3	11.3 ± 2.2	0.183
Ptt, mean ± sd	31.3 ± 12.4	30.7 ± 8.8	30.3 ± 10.0	32.9 ± 16.8	0.135
BUN, median (iqr)	17.0 (13.0, 23.0)	16.0 (12.8, 21.0)	17.0 (13.8, 21.0)	18.5 (14.0, 27.2)	< 0.001
creatinine, median (iqr)	0.9 (0.7, 1.2)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	1.0 (0.8, 1.4)	< 0.001

Table 1. All characteristics of patients with traumatic brain injury.

Logistic regression analysis of multifactorial TyG index and AKI

The TyG index was significantly associated with AKI after adjustment for multivariate analysis (Table 3). Logistic regression analyses using the TyG index as a continuous variable showed a significant correlation between AKI risk and the TyG index (model 1 OR, 2.98 [95% CI 2.15–4.14]; $P<0.001$) in models 1 and 2 (model 2 OR, 2.79 [95% CI 2-3.91]; $P<0.001$), fully adjusted model (OR, 2.07 [95% CI 1.41–3.05]; $P<0.001$). In addition, using the TyG index as a categorical variable, the highest tertile (Q3) of the TyG index was significantly associated with the risk of AKI in the unadjusted model1 (Q1 vs. Q2: OR, 2. 05 [95% CI 1.32–3.18] $p=0.001$; Q3: OR, 4.03 [95% CI 2.52–6.44] p = < 0.001) and fully adjusted models (Q1 vs. Q2: OR, 1.78 [95% CI 1.08–2.39] $p=0.023$; Q3: OR, 2.21 [95% CI 1.27–3.84] $p=0.011$). To further assess the effect of unmeasured confounders, E-value was calculated to estimate the magnitude of an unadjusted confounding variable needed to mitigate the association between TyG index and the incidence of AKI.E-value analysis showed that an unexplained confounder would need to be associated with both TyG index and AKI incidence at a odds ratio of 2.23 tomitigate the relationship between these variables, while controlling for other covariates in our model.

Restricted cubic spline regression model

Both the unadjusted and fully adjusted models showed a dose-response relationship between the TyG index and aki risk (nonlinear $P=0.677$, nonlinear $P=0.781$) (Fig. 2).

Predictive power and clinical benefit of the TyG index

We calculated the area under the ROC curve (AUC) to examine the ability of the TyG index to predict the occurrence of AKI in patients. The results showed that in patients with TBI, the TyG index predicted AKI with an AUC higher than 0.6 (IQR: 0.649 [0.602, 0.695]; numeric: 0.678 [0.631, 0.726]) (Fig. 3). In conclusion, the

Variable	Or 95ci		*P* value
Tyg	2.98 (2.15 ~ 4.14)		< 0.001
Race	1.67 (1.16 ~ 2.42)		0.006
Sex	1.45 (1.01 ~ 2.08)		0.046
age	0.98 (0.97 ~ 1)		0.011
Sepsis	4.02 (2.67 ~ 6.04)		< 0.001
Myocardial infarct	2.28 (1.19 ~ 4.39)		0.013
Congestive heart failure	1.96 (1.09 ~ 3.54)		0.025
Chronic pulmonary disease	3.02 (1.47 ~ 6.18)		0.003
Renal disease		2.07 (1.15 ~ 3.71)	0.015
Diabetes	1.6 (1.05 ~ 2.44)		0.03
Charlson comorbidity index	1.03 (0.96 ~ 1.1)		0.403
GCS	0.81 (0.76 ~ 0.86)		< 0.001
Apsiii	1.04 (1.03 ~ 1.06)		< 0.001
Sapsii	1.03 (1.01 ~ 1.05)		0.001
Oasis	1.09 (1.06 ~ 1.12)		< 0.001
Heart rate	1.02 (1.01 ~ 1.03)		0.003
Mbp	0.98 (0.97 ~ 1)		0.011
WBC		1 (0.98 ~ 1.02)	0.972
Glucose	1.01 (1 ~ 1.01)		0.001
Potassium	0.72 (0.51 ~ 1.02)		0.063
Sodium	1.06 (1.02 ~ 1.11)		0.003
Bun	1.04 (1.02 ~ 1.06)		< 0.001
Hemoglobin	0.87 (0.8 ~ 0.96)		0.003
Platelets	1 (0.99 ~ 1)		0.006
RDW		1.11 (1.05 ~ 1.19)	0.001
input1day	1 (1 ~ 1)		< 0.001

Table 2. Logistic univariate analysis.

	Model1		Model2		Model3	
Categories	OR(95%CI)	*P*-value	OR(95%CI)	*P*-value	OR(95%CI)	*P*-value
AKI incidence						
Continuous variable per 1 unit	2.98(2.15–4.14)	< 0.001	2.79(2-3.91)	< 0.001	2.07(1.41–3.05)	< 0.001
Quartile[a]						
Q1(*N* = 164)	Ref.		Ref.		Ref.	
Q2(*N* = 164)	2.05 (1.32–3.18)	0.001	1.9(1.28–3.11))	0.002	1.78(1.08–2.39)	0.023
Q3(*N* = 164)	4.03 (2.52–6.44)	< 0.001	3.61(2.24–5.83)	< 0.001	2.21(1.27–3.84)	0.005

Table 3. Logistic proportional TyG index for AKI incidence. Model 1 was unadjusted Model 2 was adjusted for sex, age and race Model 3 was adjusted for the variables in model 2 and further adjusted for GCS, apsiii, sapsii, oasis, sofa24, sepsis3, chronic pulmonary disease, myocardial infarct, renal disease, congestive heart failure, diabetes, input1day and RDW [a]TyG index Triple Quartile Q1: 7.30–8.51; Q2: 8.51–9.05; Q3: 9.05–12.10

TyG index provides some predictive value for the occurrence of AKI in patients with TI. In addition, we plotted clinical decision curves to assess the improved clinical utility of the TyG index. The results showed that the net clinical benefit of each scoring tool also improved after considering the TyG index (Fig. 4). In addition, when considering the TyG index, we also calculated the IDI as well as the NRI of the scoring tools (APSIII, OASIS, SAPSII) to analyse the effect of the TyG index on the predictive ability of the scoring tools. The IDI and the NRI are both tools for assessing the degree of improvement in the predictive ability of a response model, with greater than 0 indicating a positive improvement, and less than 0 indicating a negative improvement. The predictive ability of the scoring tool for the incidence of AKI in patients with traumatic brain injury was significantly improved ($P < 0.01$) after considering the numerical TyG index (Table 4).

Stratified analysis of the incidence of AKI according to the TyG index

We further assessed risk predictors for the primary outcome TyG index in different subgroups of patients, including age, sex, race, sepsis and diabetes (Fig. 5). No interaction was found in the above subgroups.

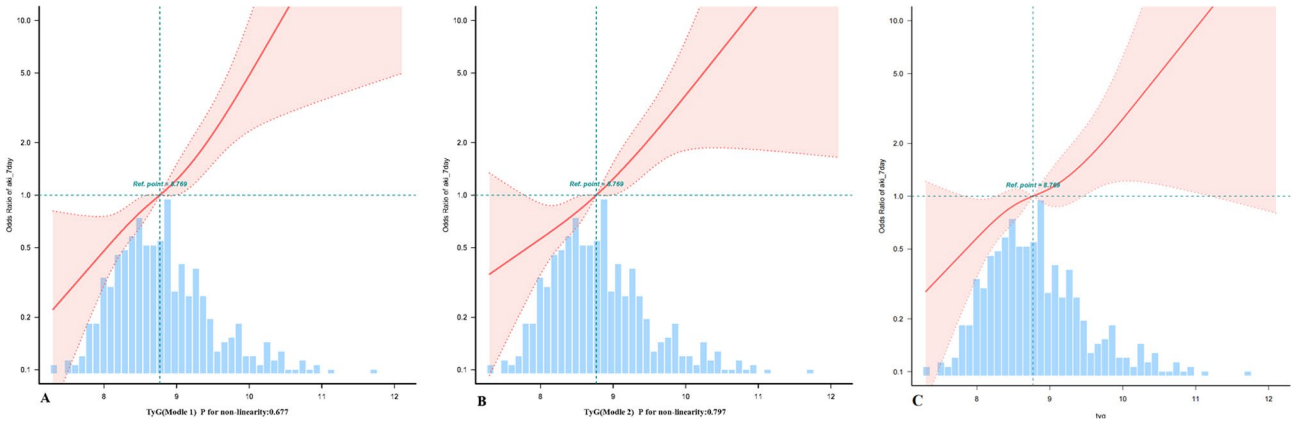

Figure 2. Restricted cubic spline curves for the TyG index hazard ratio. **A**: Model 1 was unadjusted. **B**: Model 2 was adjusted for age, sex, and race. **C**: Model 3 was adjusted for the variables in model 2 and further adjusted for GCS, apsiii, sapsii, oasis, sofa24, sepsis3, chronic pulmonary disease, myocardial infarct, renal disease, congestive heart failure, diabetes, input1day and RDW.

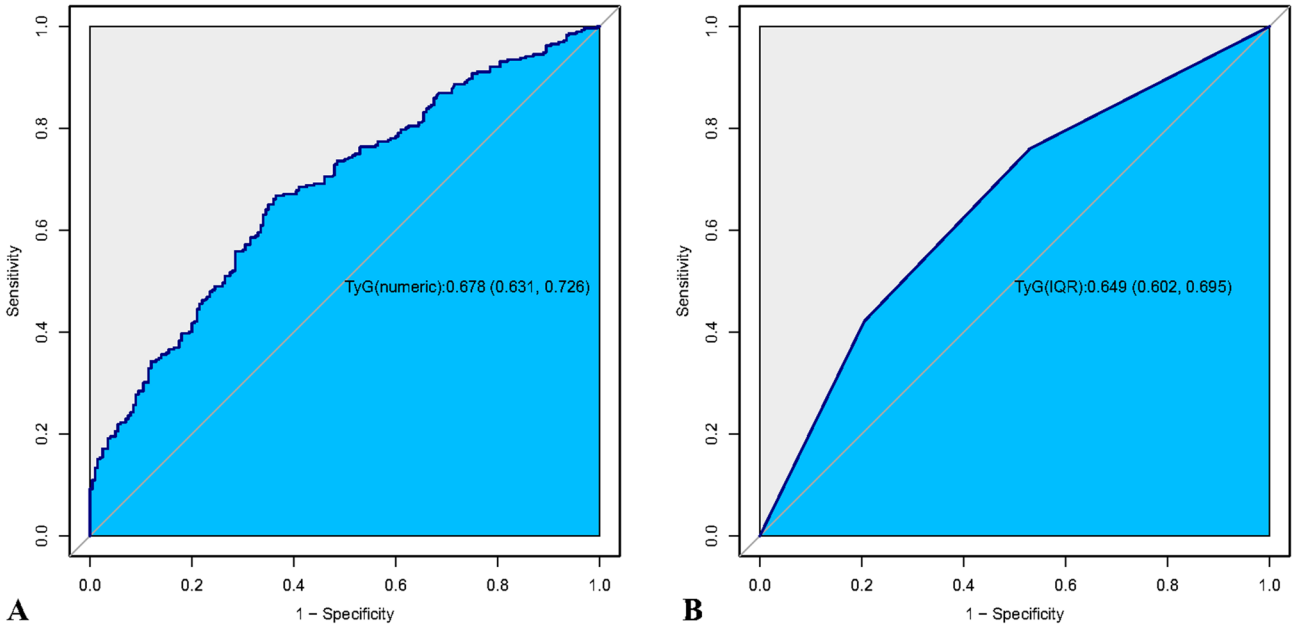

Figure 3. (**A** and **B**) ROC curve analysis of the TyG index predicts AKI.

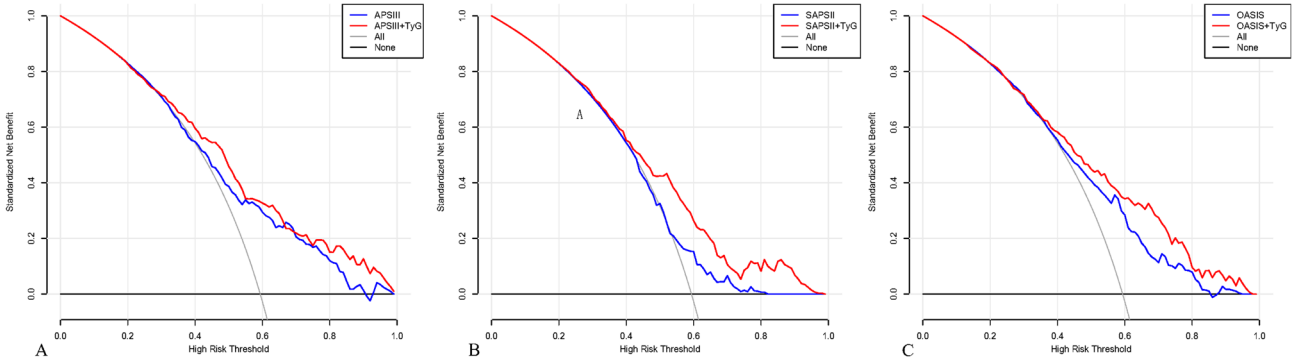

Figure 4. (**A**, **B** and **C**) Decision curve analysis of scoring tools with and without considering the TyG index (numeric).

Score	AUC [95% CI]	IDI [95%CI] (+ TyG)	*P*-value	NRI [95%CI] (+ TyG (numeric))	*P*-value
APSIII	0.696(0.650,0.742)	0.0395[0.0218,0.0572]	< 0.0001	0.4844[0.3111–0.6577]	< 0.0001
SAPSII	0.590(0.540,0.641)	0.0680[0.0458,0.0903]	< 0.0001	0.5318[0.3596–0.704]	< 0.0001
OASIS	0.686(0.649,0.733)	0.0464[0.0277,0.0651]	< 0.0001	0.4233[0.2488–0.5977]	< 0.0001

Table 4. The incremental effect of the TyG index.

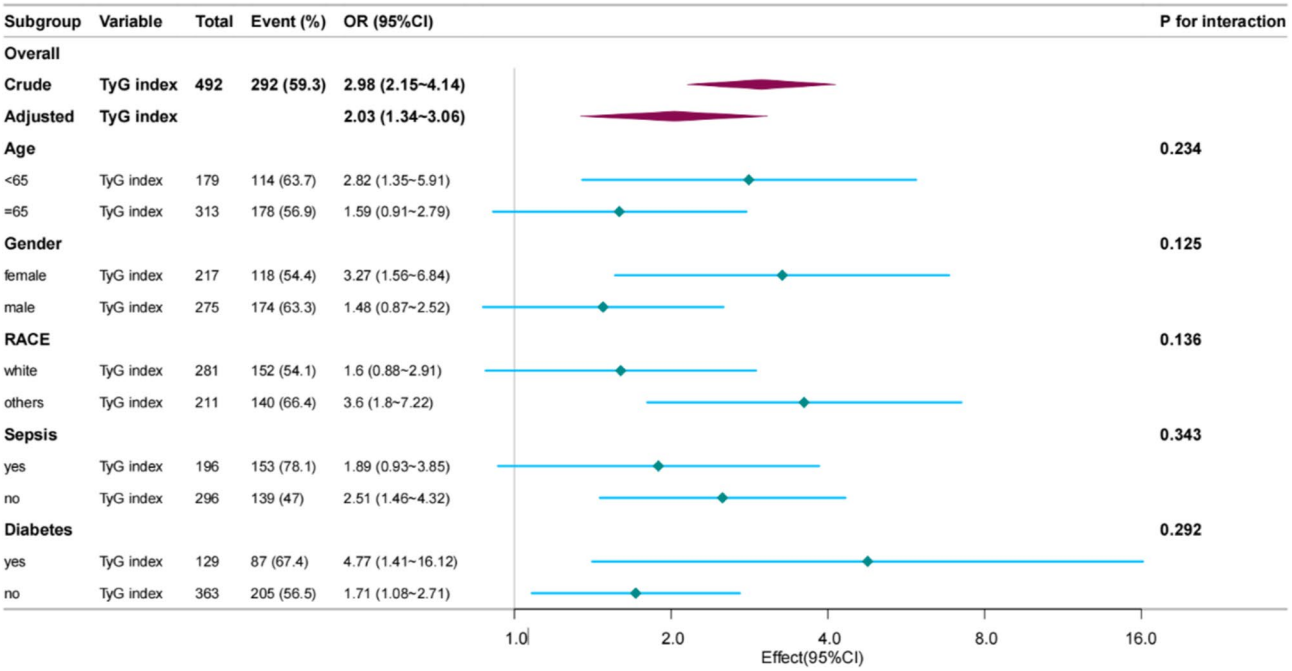

Figure 5. Stratified analysis of the incidence of AKI according to the TyG index.

Discussion

To the best of our knowledge, this study was conducted as a retrospective study to investigate the relationship between the TyG index and the occurrence of AKI in patients with TBI in the ICU. The key finding in our results suggests that ICU patients with an elevated TyG index have a higher risk of developing AKI, even after adjusting for potential confounding variables. Our findings also showed that the prevalence of AKI in patients was linearly correlated with TyG index. Most importantly, a novel, simple, and effective biomarker for early warning of AKI in ICU patients was provided by this study. TBI is a major global public health problem, and the GBD 2019 study shows a significant increase in its burden between 1990 and 2019. TBI is not only life-threatening, but also has a high rate of disability, which is particularly severe in young people, resulting in significant disability, early death and long-term socioeconomic burden. Despite advances in medical technology, prevention and management of TBI remain challenging and require multifaceted efforts[28]. Therefore, there is an urgent need to explore new biomarkers to identify patients with TBI who are at high risk of developing AKI in the ICU in order to improve their prognosis.

It has been shown that IR plays a key role in the development of traumatic brain injury and renal insufficiency, and it usually precedes the onset of these conditions[29–31]. Although homeostatic model assessment (HOMA) was once used as a simple tool for assessing IR[32], it is costly, time-consuming and may involve invasive procedures, limiting its use in clinical routine. To address this issue, Unger G et al. proposed the TyG index in 2013 as a cost-effective, efficient and easily reproducible index of IR[33].Comparison of several studies found that the TyG index outperformed the HOMA-IR in measuring IR, and therefore has greater appeal in clinical practice[34–36].

In recent years, numerous clinical studies have continued to reveal that the TyG index has demonstrated significant associations in the assessment of the health of different populations, particularly with the incidence of cerebrovascular and renal diseases and mortality. This biomarker, based on triglyceride and blood glucose levels, is gradually gaining a lot of attention in the medical community because of its simplicity and predictive value. In terms of cerebrovascular disease, Huang et al. in a prospective cohort study that included 19,924 hypertensive patients, a chronically elevated TyG index was associated with an increased risk of stroke, particularly ischemic stroke[37]. This finding means that regular monitoring of the TyG index may help to identify individuals with hypertension who are at higher risk of stroke and allow for early intervention. Chen et al. conducted a retrospective study revealing that the TyG index is an independent risk factor and an important predictor of severe disorders

of consciousness and all-cause mortality in patients with critical brain diseases[17]. And Huang et al. and Cai et al. found in their studies respectively that TyG index may have an important role in identifying patients with high all-cause mortality in hemorrhagic stroke and ischemic stroke[18,38]. In the context of renal disease, Fritz et al. found that the TyG index appeared to be associated with the risk of obesity-associated end-stage renal disease in a population-based prospective cohort study[39]. Jin et al. noted that the TyG index was associated with the risk of AKI in ICU patients[19]. Similarly, Yang et al. reported that TyG index was a reliable independent predictor of AKI incidence and adverse renal outcomes in critically ill heart failure patients[40].

Several studies have provided evidence that the TyG index can be used as a predictor of contrast-induced and critical cardiac insufficiency in patients with AKI, diabetes mellitus, or hypertension with reduced renal function, but there are limited data specifically for critically ill patients with TBI[40–43]. In our study, through in-depth mining and analysis of data from a large cohort in the United States, we analysed the significant linear correlation between TyG index and AKI in patients with severe TBI, implying that the risk of AKI showed a direct and predictable increase with increasing TyG index. This finding provides an important biomarker basis for assessing and managing AKI risk in patients with severe TBI. This finding is an important guideline for clinicians because it reminds us to pay sufficient attention to the metabolic status of patients in addition to the traditional risk factors when assessing the risk of AKI in patients with TBI.

In addition, our study explored possible associations between TyG index and pathophysiological mechanisms of TBI and AKI. The association of IR and TyG index with AKI in patients with severe TBI can be attributed to several potential mechanisms. Firstly, early glucose elevation is prevalent in patients with TBI, even on patients without diabetes, and even more so in critically ill patients[44,45], which in turn aggravates the renal burden and increases the risk of AKI. In other previous studies it has been shown that early hyperglycaemia predisposes to a poor prognosis in patients with TBI and is mainly associated with patient mortality[46–48]. There are various mechanisms by which hyperglycaemia occurs in TBI patients, the main mechanism being stress-induced elevation of blood glucose. Activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis can lead to an increase in the release of substances such as catecholamines and cytokines, which promotes the release of glucose from the liver, including through gluconeogenesis[49]. The other mechanism contributing to elevated blood glucose is IR, where impairment of the post-insulin receptor binding pathway and down-regulation of Glucose Transporter 4(GLUT-4) promotes peripheral insulin-dependent glucose uptake and leads to reduced glucose utilisation[50]. Secondly, the inflammatory response is closely associated with IR, and the inflammatory response generated after TBI can directly or indirectly damage the kidney through activation of inflammatory mediators such as cytokines and chemokines. Studies have shown that elevated plasma neutrophil gelatinase-associated lipid transport proteins associated with IR can lead to renal tubular dysfunction associated with inflammatory response[51]. In addition, IR patients are usually accompanied by increased oxidative stress, and the production of free radicals can damage renal tubular cells and vascular endothelium, affecting the normal function of the kidney and thus triggering AKI[52]. Vascular dysfunction is also an important factor, and a high TyG index may reflect vascular endothelial dysfunction, which is common in patients with TBI and can lead to reduced renal blood flow, inadequate perfusion, and an increased risk of AKI. Previous studies have shown that IR leads to reduced nitric oxide synthesis in glomerular endothelial cells[53] and that the balance between nitric oxide (NO)-dependent vasodilator effects and insulin endothelin 1-dependent vasoconstrictor effects is regulated by phosphatidylinositol 3-kinase-dependent (PI3K) and mitogen-activated protein kinase-dependent signalling in the vascular endothelium, respectively. In insulin resistance, pathway-specific impairment of PI3K-dependent signalling may lead to an imbalance between NO production and endothelin-1 secretion and result in endothelial dysfunction[54].

Meanwhile, elevated TyG index is associated with abnormalities in lipid metabolism[8], and elevated levels of free fatty acids exacerbate renal injury either through direct toxic effects or by affecting energy metabolism and inflammatory responses in the kidney[55]. In addition, IR and high TyG index affect the renal microcirculation, which can lead to abnormal activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, which in turn leads to increased blood pressure and intrarenal vasoconstriction, resulting in insufficient perfusion of renal blood flow and increasing the risk of AKI[56–58]. Neuro-renal axis interactions also play a role, with vagus nerve stimulation reducing renal ischaemia-reperfusion injury, whereas in patients with TBI it may lead to a decrease in renal blood flow and function by affecting acetylcholine[59], which may be exacerbated by IR and a high TyG index. Finally, IR affects the kidney indirectly through immunomodulatory effects such as increased inflammatory cell infiltration, which increases the risk of AKI[60]. These mechanisms interact with each other and together lead to the development of AKI. Future studies should further explore the interaction of these mechanisms and look for possible intervention strategies to reduce the risk of concurrent AKI in patients with TBI.

Study limitations

Of course, there are some limitations to our study. For example, due to limitations in the data sources, we were unable to obtain detailed metabolic parameters for all patients, which may have led to some degree of confounding by confounders, despite the use of multivariate adjustment and subgroup analyses. In addition, our study mainly focused on the assessment of the acute phase, and the impact on long-term prognosis needs to be further explored. The formula for TyG requires fasting for the collection of blood glucose and blood triglycerides, but the mimic database takes a de-identified approach to time, so we had to use blood glucose and triglycerides from the first biochemistry after admission to the ICU. This will have some impact on the results.In response to these limitations, we suggest that future studies should focus more on the importance of real-time monitoring of TyG changes in order to more accurately assess its role in the development of TBI and AKI. Meanwhile, we are preparing to conduct a multicentre, large sample size prospective study our findings and further explore the mechanism of association of TyG index with TBI and AKI.

Conclusion

In summary, our study reveals the importance of TyG index in assessing the risk of AKI in patients with severe TBI. This finding not only enriches our understanding of the pathogenesis of TBI and AKI, but also provides clinicians with a new risk assessment tool and basis for the selection of treatment strategies.

Data availability

The data utilized in this investigation was sourced from the Medical Information Mart for Intensive Care IV (MIMIC-IV), which is accessible at the following link: https://mimic-iv.mit.edu. To gain access to the data, one must be an authenticated user, complete the required training, and adhere to the project's data usage agreement. Any request for access to these datasets should be directed to PhysioNet (https://physionet.org/) with the reference DOI: 10.13026/s6n6-xd98. It is essential to note that the dataset has specific licensing and access restrictions in place.

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Author contributions

J.H designed the study. J.H extracted, collected and analysed the data and wrote the manuscript.CC.S prepared the tables and figures. Y.X proofread the data. JB.W, Y.F and LL.L reviewed the results and interpreted the data. GS.G provided professional advice on the revision of the manuscript as well as funding for the study. DH.K reviewed and revised the manuscript and funded the study. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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Abbreviations

TyG index	Triglyceride-Glucose index
AKI	Acute Kidney Injury
ICU	Intensive Care Unit
TBI	Traumatic Brain Injury
MIMIC-IV	Medical Information Mart for Intensive Care IV
ROC	Receiver Operating Characteristic
IR	Insulin Resistance
FBG	Fsting Blood Glucose
TG	Triglyceride
BIDMC	Beth Israel Deaconess Medical Center
CITI	Cooperative Institutional Training Initiative
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	Based on the International Classification of Diseases, Ninth Revision
SQL	Structured Query Language
BMI	Body Mass Index
SBP	Systolic Blood Pressure
MBP	Mean Blood Pressure
Spo2	Oxygen Saturation
RDW	Red Blood Cell Distribution Width
BUN	Blood Urea Nitrogen
WBC	White Blood Cell Count
PTT	Plasminogen Time
APSIII	Acute Physiology Score III
OASIS	Oxford Acute Severity of Illness Score
SAPSII	Simplified Acute Physiology Score
SOFA	Sequential Organ Failure Score
SCr	Serum Creatinine
SD	Standard Deviation
ANOVA	Analysis of Variance
IQR	Interquartile Range
ORs	Odds Ratios
IDI	Integrated Discriminant Improvement
NRI	Net Weight Improvement Index
CI	Confidence Intervals
AUC	Area Under the ROC Curve
HOMA	Homeostatic Model Assessment
HPA	Hypothalamic-Pituitary-Adrenal
GLUT-4	Glucose Transporter 4
NO	Nitric Oxide
PI3K	Phosphatidylinositol 3-kinase-dependent