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# The relationship between serum fibrinogen-like protein 2 concentrations and 30-day mortality of patients with traumatic brain injury

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ABSTRACT

*Background:* Fibrinogen-like protein 2 (FGL2) is an inflammatory procoagulant protein. We discerned the impact of serum FGL2 on trauma severity and 30-day mortality in patients with traumatic brain injury (TBI).
*Methods:* A total of 114 severe TBI patients were subjected to assessment of trauma severity using the Glasgow coma scale (GCS). Measurement of the serum concentrations of FGL2 was done. 114 matched control subjects for their age and sex were included for comparison of serum concentration of FGL2.
*Results:* The concentration of FGL2 was dramatically increased in the patients as compared with the control subjects. FGL2 concentration was inversely correlated with GCS score among the patients. The non-survivors within 30 days exhibited substantially higher FGL2 concentrations than the alive. FGL2 concentrations discriminated the patients at risk of 30-day death with significantly high area under receiver operating characteristic curve. Serum FGL2 emerged as an independent predictor for mortality and overall survival at 30 days after head trauma.
*Conclusions:* Serum FGL2 is a promising biomarker for assessing the severity and prognosis in severe TBI.

## 1. Introduction

Severe traumatic brain injury (sTBI) is one of the most common causes of adult death and disability worldwide [1–5]. Reportedly, 20–30% of sTBI patients die within 30 days after head trauma and most sTBI survivors are permanently disabled [1–5]. The Glasgow Coma Scale (GCS) is the most commonly used system for classifying TBI severity [6–8]. The mechanisms underlying secondary brain injury after trauma are rather complicated and comprise free radical damage, inflammatory infiltration, calcium overload, endothelial injury and platelet activation [9–12]. Fibrinogen-like protein 2 (FGL2) is encoded by the FGL2 gene and formerly found to be expressed in macrophages, endothelial cells and trophoblastic cells. Functionally, it acts as an inflammatory procoagulant protein, directly activating pro-thrombin and igniting the coagulation process [13–15]. Moreover, FGL2 participates in several inflammatory and procoagulant diseases such as fulminant hepatitis, kidney auto-transplantation reaction, severe acute pancreatitis, acute myocardial ischemic-reperfusion injury, rheumatoid arthritis and osteoarthritis [16–21]. Intriguingly, FGL2 can be produced from animal brain tissues after ischemic or hemorrhagic injury [22–24]. Of note, in a recent study, serum FGL2 concentrations tended to strongly correlate with cerebral infarct size in rats with acute cerebral ischemic-reperfusion.

## 2. Materials and methods

### 2.1. Study population

This study is a prospective, observational study conducted on a group of adult patients (≥18 y) with diagnosis of sTBI (GCS < 9 points, not under the influence of pharmacologic agents or alcohol) admitted within the first 6 h after head trauma. They were consecutively recruited from the Yiwu Central Hospital, China between September 2014 and October 2017. We required that injury severity score was ≤9 points in non-cranial aspects among the enrolled patients. We also excluded those patients with surgery or trauma with recent 4 weeks, presentation with ischemic or hemorrhagic stroke or other neurological diseases, use of antiplatelet or anticoagulant medication, obtainment with immunosuppressive therapy, acute or chronic infections at study enrollment or presence of other systemic diseases such as diabetes mellitus, hypertension, uremia, liver cirrhosis, malignancy and chronic heart or lung disease. Healthy volunteers were enrolled as the controls. The study was performed with the approval of the ethics committee at our hospital. The controls and the relatives of all patients wrote the

*Abbreviations:* GCS, Glasgow coma scale; TBI, traumatic brain injury; FGL2, fibrinogen-like protein 2

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consent to participate in the current study after the study protocol was informed. The study adhered to the ethical conduct of research involving human subjects by World Medical Association Declaration of Helsinki.

### 2.2. Assessment

In each patient, were recorded the following variables: age, gender, vital signs, time from trauma to admission, comorbidities, details of drug usage and pupillary reactivity. We classified TBI severity by the postresuscitation GCS. Head computerized tomography (CT) scans were done according to radiological protocol, and the recorded variables included abnormal cisterns, midline shift, subarachnoid hemorrhage and brain lesion according to the Marshall CT classification [25]. CT lesion according to Marshall classification [25] is as follows: Class I (not visible pathology), Class II (cisterns are present and midline shift < 5 mm and there is not lesion > 25 $cm^3$), Class III (cisterns are compressed and midline shift < 5 mm and there is not lesion > 25 $cm^3$), Class IV (midline shift > 5 mm and there is not lesion > 25 $cm^3$), Class V (evacuated lesion) or Class VI (lesion > 25 $cm^3$ not surgically evacuated). We used mortality at 30 days as endpoint.

### 2.3. Immune analysis

We obtained the peripheral venous blood from the patients at admission and from controls at study entry. Blood samples were collected by standard venipuncture through a vein in the antecubital fossa into one serum separator tube. All samples were centrifuged, aliquoted, and stored at −80 °C until serum concentration determinations. Afterwards, every 3 months, the same personnel, without access to clinical data, quantified serum FGL2 concentrations in duplicate samples with a quantitative sandwich enzyme-linked immunosorbent assay kit (USBiological, USA). Two measurements were averaged for statistical analysis.

### 2.4. Statistical methods

Statistical analyses were conducted with Statistical Package for the Social Sciences ver 19.0, Fig.s were developed using GraphPad Prism ver 5.0 and receiver operating characteristic (ROC) curve analysis was performed by MedCalc 9.6.4.0. For continuous variables, the normality of data distribution was assessed by the Kolmogorovor-Smirnov test or Shapiro-Wilk test. Because all continuous variables were verified to be non-normally distributed, they were shown as median (the upper - lower quartiles). A Mann-Whitney *U* test was run to determine if there was difference in serum FGL2 concentration. Categorical variables were presented as counts (percentage) and their comparisons were performed using $\chi^2$ test or Fisher exact test.

We used the Kaplan–Meier method to estimate 30-day overall survival. Using the log-rank test, intergroup difference of survival time was compared. In order to determine the variables independently associated with 30-day overall survival and mortality, we configured the multivariate Cox's proportional hazard model and binary Logistic regression model. At first, we conducted the univariate Cox's proportional hazard analysis or binary Logistic regression analysis, and afterwards, we included in multivariate analysis the statistically significant variables in the univariate analysis. We calculated the odds ratio (OR) or hazard ratio (HR) values and 95% confidence intervals to measure the association of variables with mortality. ROC curve was constructed with serum concentrations of FGL2 as prognostic variable and 30-day death as classification variable. To select cut-off prognostic value of serum FGL2 concentration, Youden J index was used. The area under ROC curve (AUC) and 95% CI were reported. Correlation between continuous variables was analyzed using coefficient of Spearman. A $P < .05$ was considered as statistically significant.

## 3. Results

### 3.1. Study population characteristics

Initially, we enrolled a total of 150 adult patients with sTBI admitted within the first 6 h after head trauma, whose injury severity score was ≤ 9 points in non-cranial aspects. Afterwards, in accordance to exclusion criteria, we excluded thirty-two patients with surgery or trauma with recent 4 weeks (4 cases), ischemic or hemorrhagic stroke or other neurological diseases (6 cases), use of antiplatelet or anticoagulant medication (6 cases), immunosuppressive therapy (3 cases), acute or chronic infections at study enrollment (5 cases) or presence of other systemic diseases (8 cases). Also, two patients were lost to follow up, 1 patient refused to participate and one patient had an unavailable sample. Eventually, one hundred and fourteen patients were analyzed. Alternatively, we recruited 114 healthy controls. In terms of gender percentage and age, there were no statistical differences between the controls and the patients.

The sTBI patients, whose age ranged from 18 to 76 y, had a median age of 43 y (the upper - lower quartiles, 30–56 y), 70 being males and 44 being females. Traumatic causes included automobile/motorcycle in 53 patients (46.5%), fall/jump in 40 patients (35.1%) and others in 21 patients (18.4%). The patients were admitted from 0.5 to 6.0 h after trauma, with a median value of 2.1 h (1.6–2.7 h). As regards trauma severity, we recorded the median postresuscitation GCS score of 5 (the upper - lower quartiles, 4–7; range, 3–8). With respect to pupillary reaction, admission unreactive pupils appeared in a total of 49 patients (43.0%). On the initial CT examinations, CT classification 5 or 6 was revealed in 47 patients (41.2%), a total of 51 patients (44.7%) exhibited abnormal cisterns, there was midline shift > 5 mm in fifty-eight patients (50.9%) and 67 patients (58.8%) presented with traumatic subarachnoid hemorrhage. Noninvasive blood pressure measurement showed that systolic arterial pressure ranged from 70 to 152 mmHg (median, 121 mmHg; the upper - lower quartiles, 92–141 mmHg) and median diastolic arterial pressure was 72 mmHg (the upper - lower quartiles, 56–90 mmHg; rang, 45–102 mmHg). Via laboratory test, serum C-reactive protein concentrations ranged from 6.9 to 22.1 mg/L, with a median value of 13.3 mg/L (the upper - lower quartiles, 10.8–16.1 mg/L); blood glucose concentrations ranged from 2.5 to 25.8 mmol/L, with a median value of 10.3 mmol/L (the upper - lower quartiles, 8.8–13.7 mmol/L); blood white blood cell count ranged from 3.9 to 15.2 × $10^9$/L, with a median value of 7.6 × $10^9$/L (the upper - lower quartiles, 5.5–9.6 × $10^9$/L).

### 3.2. Serum FGL2 concentrations and its correlation with GCS scores

Serum FGL2 concentrations ranged from 25.2 to 769.2 ng/mL (median, 254 ng/ml; the upper - lower quartiles, 163.6–322.4 ng/mL) in the patients. Among the controls, its median concentrations were 45.0 ng/mL (the upper - lower quartiles, 26.8–56.4 ng/mL) and its concentrations ranged from 5.0 to 79.5 ng/mL. By comparison, serum FGL2 concentrations were substantially in the patients than in the controls ($P < .001$).

Bivariate correlation analysis showed there was a negative correlation between serum concentrations of FGL2 and GCS scores ($r = -0.539$, $P < .001$; Fig. 1). Alternatively, serum FGL2 concentrations were dichotomized based on its median value (254 ng/mL). Using bivariate analysis (Table 1), we found that, as compared to the patients with FGL2 concentrations < 254 ng/mL, those with FGL2 concentrations > 254 ng/mL exhibited lower GCS scores, and a higher proportion of unreactive pupils, CT classification 5 or 6, abnormal cisterns, and midline shift > 5 mm. Moreover, the preceding significant parameters were further analyzed in the multivariate model and it was demonstrated that GCS score emerged as an independent risk factor for serum FGL2 concentrations > 254 ng/mL (OR = 0.574, 95% CI = 0.414–0.795, $P = .001$).

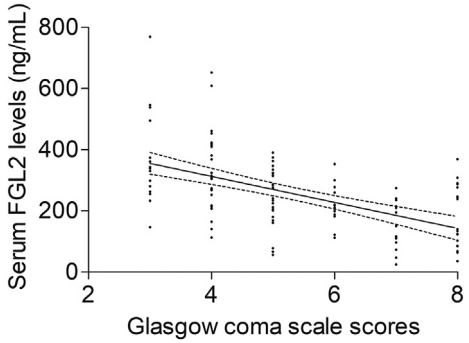


**Fig. 1.** The intimate and inverse correlation of serum fibrinogen-like protein 2 (FGL2) concentrations with Glasgow coma scale (GCS) scores among traumatic brain injury patients. Using Spearman test, serum FGL2 concentrations were strongly associated with GCS scores ($r = -0.539$, $P < .001$).

**Table 1**
The factors related to serum fibrinogen-like protein 2 concentrations after head trauma.

| | Odds ratio | 95% CI | *P* value |
|---|---|---|---|
| Gender | 1.562 | 0.731–3.340 | NS |
| Age (y) | 1.018 | 0.995–1.041 | NS |
| Mechanisms of injury | 0.831 | 0.510–1.354 | NS |
| GCS scores | 0.509 | 0.382–0.677 | < 0.001 |
| Unreactive pupils | 12.549 | 5.049–31.189 | < 0.001 |
| Marshall CT classification 5 or 6 | 4.223 | 1.987–9.400 | < 0.001 |
| Abnormal cisterns | 2.979 | 1.383–6.415 | 0.005 |
| Midline shift > 5 mm | 2.352 | 1.110–4.985 | 0.026 |
| Traumatic SAH | 1.931 | 0.906–4.116 | NS |
| Admission time (h) | 0.924 | 0.680–1.256 | NS |
| Plasma-sampling time (h) | 1.042 | 0.801–1.356 | NS |
| Systolic arterial pressure (mmHg) | 0.989 | 0.976–1.002 | NS |
| Diastolic arterial pressure (mmHg) | 0.994 | 0.975–1.012 | NS |
| Serum C-reactive protein (mg/L) | 1.081 | 0.971–1.203 | NS |
| Blood glucose (mmol/L) | 1.020 | 0.923–1.126 | NS |
| Blood white blood cell count ($\times 10^9$/L) | 1.022 | 0.871–1.199 | NS |

Univariate binary regression analysis was conducted to estimate the odds ratio and 95% CI values associated with serum fibrinogen-like protein 2 concentrations > 253.9 ng/mL. GCS indicates Glasgow Coma Scale; CT, computerized tomography; SAH, subarachnoid hemorrhage.

### 3.3. Mortality analysis

Posttraumatic 30–day mortality was 23.7% (27/114). Table 2 shows that lower GCS scores, older age, a higher proportion of unreactive pupils, CT classification 5 or 6, abnormal cisterns, midline shift > 5 mm and traumatic subarachnoid hemorrhage, higher blood glucose concentrations and higher serum concentrations of C-reactive protein and FGL2 were dramatically associated with increasing risk of death within 30 days following trauma. Moreover, when the above-mentioned variables were incorporated into the binary logistic regression model, it was verified that age (OR = 1.055, 95% CI = 1.005–1.110, $P = .031$), serum FGL2 (OR = 1.012, 95% CI = 1.003–1.018, $P = .011$) and GCS score (OR = 0.198, 95% CI = 0.071–0.551, $P = .003$) remained as the independent predictors for 30-day mortality after head trauma.

In order to assess whether serum FGL2 concentrations could significantly differentiate between the deceased and the alive within 30 days after trauma, we constructed a ROC curve. Subsequently, calculated AUC of serum FGL2 as an indicator for prognosis of 30-day mortality was 0.810 (95% CI = 0.726–0.878, $P < .001$; Fig. 2). In addition, an optimal cutoff value (252.6 ng/mL) was chosen, which predicted 30-day mortality with a sensitivity of 85.2% and a specificity of 60.9%, and the corresponding Youden J index was 0.461.

**Table 2**
The factors related to 30-day mortality after traumatic brain injury.

| | Odds ratio | 95% CI | *P* value |
|---|---|---|---|
| Gender | 0.727 | 0.303–1.745 | NS |
| Age (y) | 1.045 | 1.016–1.076 | 0.002 |
| Mechanisms of injury | 1.347 | 0.768–2.364 | NS |
| GCS scores | 0.190 | 0.091–0.397 | < 0.001 |
| Unreactive pupils | 19.840 | 5.478–71.853 | < 0.001 |
| Marshall CT classification 5 or 6 | 6.349 | 2.399–16.803 | < 0.001 |
| Abnormal cisterns | 5.161 | 1.964–13.562 | 0.001 |
| Midline shift > 5 mm | 6.233 | 2.158–18.003 | 0.001 |
| Traumatic SAH | 13.393 | 2.987–60.047 | 0.001 |
| Admission time (h) | 0.823 | 0.546–1.239 | NS |
| Plasma-sampling time (h) | 0.851 | 0.604–1.200 | NS |
| Systolic arterial pressure (mmHg) | 1.002 | 0.987–1.017 | NS |
| Diastolic arterial pressure (mmHg) | 1.010 | 0.988–1.032 | NS |
| Serum C-reactive protein (mg/L) | 1.181 | 1.043–1.337 | 0.009 |
| Serum FGL 2 (ng/mL) | 1.012 | 1.007–1.018 | < 0.001 |
| Blood glucose (mmol/L) | 1.185 | 1.041–1.341 | 0.012 |
| Blood white blood cell count ($\times 10^9$/L) | 1.031 | 0.855–1.243 | NS |

Univariate binary regression analysis was conducted to estimate the odds ratio and 95% C) values associated with 30-day mortality. GCS indicates Glasgow Coma Scale; CT, computerized tomography; SAH, subarachnoid hemorrhage; FGL2, fibrinogen-like protein 2.

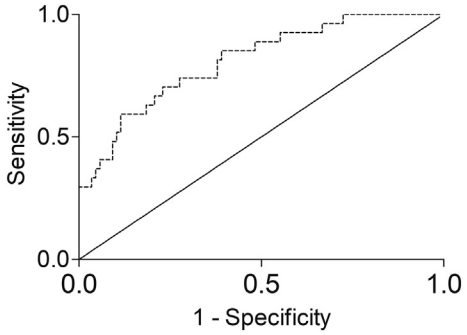


**Fig. 2.** The strong discriminatory ability of serum fibrinogen-like protein 2 (FGL2) concentrations for patients at risk of 30-day death after traumatic brain injury under receiver operating characteristic (ROC) curve. Area under ROC curve of serum FGL2 as an indicator for prognosis of 30-day mortality was 0.810 (95% confidence interval = 0.726–0.878, $P < .001$); also, an optimal cutoff value (252.6 ng/mL) predicted 30-day mortality with a sensitivity of 85.2% and a specificity of 60.9%, and the corresponding Youden J index was 0.461.

### 3.4. Survival analysis

During 30-day follow-up, the mean overall survival time was 25.1 days (95%CI, 23.4–26.8 days) among all patients. Just as listed in Table 3, lower GCS scores, older age, a higher percentage of unreactive pupils, CT classification 5 or 6, abnormal cisterns, midline shift > 5 mm and traumatic subarachnoid hemorrhage, higher blood glucose concentrations and higher serum concentrations of C-reactive protein and FGL2 had a strong association with shortened overall survival time. Further, the aforementioned parameters were included into a multivariate model and subsequently, we found that the predictors independently related to 30-day overall survival were age (HR = 1.028, 95% CI = 1.002–1.055, $P = .041$), serum FGL2 (HR = 1.005, 95% CI = 1.001–1.009, $P = .004$) and GCS score (HR = 0.401, 95% CI = 0.249–0.661, $P = .001$).

Additionally, serum FGL2 concentrations were dichotomized based on its median value (254 ng/mL). In Fig. 3, patients with serum FGL2 concentrations > 254 ng/mL had significantly shorter 30-day overall survival time than those with serum FGL2 concentrations lower than 254 ng/mL (mean, 21.7 days; 95%CI, 18.9–24.6 days vs. mean, 28.5 days; 95%CI, 27.1–29.8 days; $P < .001$).

**Table 3**
The factors related to 30-day overall survival following craniocerebral head.

| | Hazard ratio | 95% CI | *P* value |
|---|---|---|---|
| Gender | 0.754 | 0.353–1.610 | NS |
| Age (y) | 1.036 | 1.012–1.060 | 0.003 |
| Mechanisms of injury | 1.278 | 0.787–2.077 | NS |
| GCS scores | 0.313 | 0.199–0.493 | < 0.001 |
| Unreactive pupils | 14.009 | 4.210–46.661 | < 0.001 |
| Marshall CT classification 5 or 6 | 5.371 | 2.266–12.727 | < 0.001 |
| Abnormal cisterns | 4.297 | 1.814–10.175 | < 0.001 |
| Midline shift > 5 mm | 5.087 | 1.924–13.451 | 0.001 |
| Traumatic SAH | 10.963 | 2.594–46.332 | 0.001 |
| Admission time (h) | 0.851 | 0.594–1.220 | NS |
| Plasma-sampling time (h) | 0.873 | 0.650–1.173 | NS |
| Systolic arterial pressure (mmHg) | 1.002 | 0.989–1.016 | NS |
| Diastolic arterial pressure (mmHg) | 1.008 | 0.990–1.029 | NS |
| Serum C-reactive protein (mg/L) | 1.154 | 1.047–1.272 | 0.004 |
| Serum FGL 2 (ng/mL) | 1.008 | 1.006–1.011 | < 0.001 |
| Blood glucose (mmol/L) | 1.164 | 1.046–1.299 | 0.005 |
| Blood white blood cell count ($\times 10^9$/L) | 1.017 | 0.850–1.212 | 0.860 |

Univariate binary regression analysis was conducted to estimate the hazard ratio and 95% C) values associated with 30-day overall survival. GCS indicates Glasgow Coma Scale; CT, computerized tomography; SAH, subarachnoid hemorrhage; FGL2, fibrinogen-like protein 2.

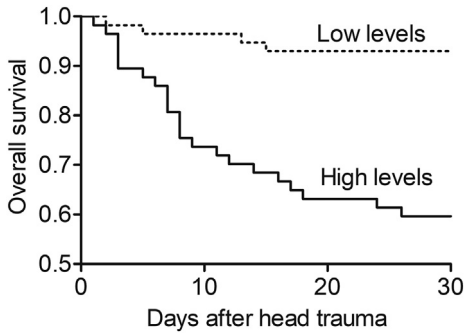


**Fig. 3.** The substantial influence of serum fibrinogen-like protein 2 (FGL2) concentrations on 30-day overall survival time in accordance with survival curve in patients with traumatic brain injury. Serum FGL2 concentrations were dichotomized based on its median value (254 ng/mL). Patients with serum FGL2 concentrations > 254 ng/mL had significantly shorter 30-day overall survival time than those with serum FGL2 concentrations lower than 254 ng/mL (mean, 21.7 days; 95%CI, 18.9–24.6 days vs. mean, 28.5 days; 95%CI, 27.1–29.8 days; P < .001).

## 4. Discussion

FGL2 is a member of the fibrinogen related protein superfamily. Also, it has been identified as a new procoagulant and inflammatory factor. Formerly, it is found to be derived from cells outside central nervous system [13–15]. A recent study showed that this protein could be expressed significantly in ischemic brain tissues of rats with acute cerebral ischemic-reperfusion injury [22]. In intracerebral hemorrhage experiments, FGL2 expression has been regarded as a marker for reflecting the extent of inflammatory response and some proteins might exert a protective or detrimental effect on neuronal cells via modulating FGL2 expressions [23,24]. Up to now, whether FGL2 can be secreted from traumatized brain tissues remains unclear. To the best of my knowledge, our study, for the first time, investigated FGL2 in TBI. Our results showed that serum FGL2 concentrations rose in early phase (almost within 6 h after head trauma). Similarly, in acute cerebral ischemic reperfusion rats, FGL2 mRNA and protein expressions were markedly enhanced in cerebral tissues [22]. Simultaneously, serum concentrations of this protein were elevated greatly after acute cerebral ischemic-reperfusion injury in rats [22]. The preceding data, therefore, support the notion that FGL2 might be, at least partly, derived from injured human brain tissues.

Since FGL2 could be released from injured brain tissues, what are its effects on earth? Based on the previous findings that FGL2 is characterized by the strong inflammatory and procoagulant functions [16–21], its harmful effects have been validated in animal experiments [23,24]. Nevertheless, whether antagonizing FGL2 could protect neuronal cells and even improve neurologic function warrants to be further studied. However, a recent study reported an intriguing finding that elevated serum FGL2 concentrations were highly correlated with cerebral infarct size in acute cerebral ischemic-reperfusion injury rats [22], indicating FGL2 might reflect the extent of brain injury. In line with the preceding data [22], our study demonstrated that serum FGL2 concentrations were substantially increased with decreasing GCS scores. Moreover, we dichotomized the serum FGL2 concentrations according to its median value and consequently serum FGL2 concentration was considered as a categorical variable. Afterwards, the binary logistic regression model was applied in the current study. The statistical analysis showed that GCS was an independent risk factor for higher serum FGL2 concentration. Such data would supply an enough statistical powder to draw a confirmatory conclusion that serum FGL2 concentrations were significantly inversely correlated with GCS scores. Clearly, GCS can accurately assess clinical severity of head trauma, when patients are not influenced by pharmacologic agents or alcohol [6–8]. Our study had excluded those patients with influence of pharmacologic agents or alcohol. Overall, serum FGL2 concentrations might be strongly correlated with trauma severity and possess the ability to reflect the extent of traumatized brain injury.

Based on the preceding analyses, undoubtfully, it was deduced that serum FGL2 might be a prognostic biomarker for TBI. In the current study, we underwent a 30-day follow up and considered death at 30 days as endpoint. With respect to statistical methods, we regarded 30-day mortality and overall survival as the two prognostic variables, so that the conclusion could be more reliable and scientific. As expected, besides age and GCS score, which are the two most common determinants for prognosis of head trauma [6–8], serum FGL2 became an independent predictor for 30-day mortality and overall survival. On the other hand, we constructed a ROC curve and showed an interesting finding that serum FGL2 concentrations could significantly discriminate the patients at risk of 30-day death following head trauma. Hence, the current study provided evidence that serum FGL2 might be a promising prognostic biomarker for TBI.

However, our study only enrolled a total of 114 patients and therefore, the conclusion needs to be validated in a large sample size. In addition, we did a short-term follow-up and thereby whether serum FGL2 could be a useful biomarker for long-term prognosis of head trauma warrants to be further investigated. Also, all enrolled patients were Chinese and consequently, it remains to be explored whether such a conclusion could be generalized to other races.

## 5. Conclusions

Our study confirmed that increases of serum FGL2 concentrations at admission has a close relation to the severity and 30-day mortality of head trauma, substantializing FGL2 as a potential prognostic marker for TBI.

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