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# A prospective study on serum secreted protein acidic and rich in cysteine-like 1 as a prognostic marker for severe traumatic brain injury

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ABSTRACT

*Background:* Secreted protein acidic and rich in cysteine-like 1 (SPARCL1) regulates synaptic stability with upregulation throughout axonal regeneration. Our study aims to determine the correlation of serum SPARCL1 concentrations with the severity and in-hospital mortality of severe traumatic brain injury (sTBI).

*Methods:* A total of 102 consecutively recruited patients admitted for sTBI and 102 randomly selected healthy controls were included in this observational prospective study. Serum SPARCL1 concentrations were measured and correlated with Glasgow coma scale (GCS) scores and in-hospital mortality using multivariate analysis.

*Results:* Compared with controls (median, 0.22 ng/ml; interquartile range, 0.19–0.41 ng/ml), patients had significantly higher SPARCL1 concentrations (median, 3.29 ng/ml; interquartile range, 1.88–4.37; $P < 0.001$). There was an independently correlation between SPARCL1 concentrations and GCS scores ($t = -7.011$, $P < 0.001$). We found a high area under receiver operating curve (AUC) of serum SPARCL1 concentrations to predict in-hospital mortality (AUC, 0.822; 95% confidence interval, 0.734–0.891). In the multiple logistic regression analysis, serum SPARCL1 concentrations > 3.29 ng/ml was independently associated with in-hospital mortality (odds ratio = 10.052, 95% confidence interval = 1.918–52.686, $P = 0.006$).

*Conclusions:* The novel findings of our study are that sTBI patients had an increase of serum SPARCL1 concentrations, and that there is an association between high serum SPARCL1 concentrations and sTBI mortality or trauma severity.

## 1. Introduction

Severe traumatic brain injury (sTBI) is one of the most common forms of trauma and can result in resources consumption, disabilities, and deaths [1–6]. TBI leads to primary and secondary brain injuries. The former is caused on account of physical forces at the moment of impact and the latter, occurring at hours or days following TBI, is characterized by neuroinflammation and brain oxidative damage [7–10]. Matricellular proteins in the brain play a crucial role in developmental processes, and meanwhile they are involved in the support of neuronal integrity [11–14]. Secreted protein acidic and rich in cysteine-like 1 (SPARCL1), also known as HEVIN, is a protein that in humans is encoded by the SPARCL1 gene [15–17]. This protein is broadly distributed in several tissues, such as the bone, cartilage, and kidney [15–17]. Also, it is located in the cerebral cortex and hippocampus of developing and adult mice as well as can be specifically expressed by radial glia and astrocytes in the cerebral cortex and brainstem of neonatal mice [18,19]. Under brain injury, SPARCL1 had an impact on synaptic stability and was upregulated during axonal regeneration [19]. Intriguingly, it was expressed in rat brain after ischemic or hemorrhagic damage [20]. More recently, serum SPARCL1 concentrations were revealed to be independently associated with human ischemic stroke severity assessed by the National Institutes of Health Stroke Scale (NIHSS) on hospital admission [21]. Consequently, we speculated that serum SPARCL1 might be a potential prognostic biomarker for brain injury. This study was designed to detect serum SPARCL1 concentrations in a group of sTBI patients and ascertained the relationship between APRCL1 concentrations and severity in addition to in-hospital mortality.

*Abbreviations:* CT, computerized tomography; GCS, Glasgow coma scale; sTBI, severe traumatic brain injury; SPARCL1, secreted protein acidic and rich in cysteine-like 1; NIHSS, National Institute of Health Stroke Scale

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## 2. Materials and methods

### 2.1. Design and subjects

This observational prospective study was performed with the written informed consent from subject legal guardians at the Shengzhou People's Hospital from China after the approval by the Institutional Review Board of our hospital from September 2014 to September 2017. The investigation was conducted in compliance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. sTBI patients were consecutively enrolled. We estimated trauma severity in accordance to Glasgow Coma Scale (GCS) and sTBI was defined as GCS score < 9 while patients were not influenced by pharmacologic agents or alcohol. We excluded patients with age < 18 y, pregnancy if females, inflammatory or malignant disease, use of antiplatelet or anticoagulant medication, previous intracerebral hemorrhage or subarachnoid hemorrhage, injury severity score in non-cranial aspects > 9 points or time from trauma to admission > 6 h. Healthy volunteers identified as controls did not exhibit clinical symptoms or sign of any diseases.

### 2.2. Variables recorded

We recorded the following variables in each patient: age, gender, time from trauma to admission, comorbidities, leukocytes, glycemia, traumatic cause, GCS score, details of drug usage, pupillary reactivity. An emergency head computerized tomography (CT) was done in the emergency department in accordance with the protocol of radiological department. The head CT scan was usually carried out within 30 min after the patient was first examined by an emergency physician. The CT examination involved the acquisition of parenchymal and bone window images. All head CT scans were reviewed for signs of head trauma by a radiologist inaccessible to the patients' information. The positive trauma-related cerebral lesions included skull-cap fracture, skull-base fracture, epidural hematoma, subdural hematoma, traumatic subarachnoid hemorrhage, cerebral hematoma, brain contusion and pneumocephalus. Abnormal cisterns and midline shift were also recorded. Brain lesion was described according to the Marshall CT classification [22]. The study end-point was in-hospital mortality.

### 2.3. Blood sample collection and serum SPARCL1 analysis

Blood samples were collected for the patients at the moment of admission and for the controls at the study entrance. Serum SPARCL1 concentrations were detected in duplicate using enzyme-linked immunosorbent assay (Abcam) by the same technician blinded to clinical information. All determinations were in batches performed every 3 months. Two measurements were averaged for data process.

### 2.4. Statistical methods

Medians and interquartile ranges were utilized to report continuous variables, as well as frequencies and percentages to report categorical variables. Wilcoxon-Mann-Whitney test or Kruskal-Wallis H test was done to compare continuous variables between groups, and $\chi^2$ test or Fisher's exact test to compare categorical variables. Bivariate correlation was analyzed using Spearman's rank correlation test. Multivariate linear regression analysis was done for adjusting other confounding factors. Binary logistic regression model was conFig.d to perform multivariate analysis. We calculated odds ratio (OR) and 95% confidence interval (CI). Receiver operator characteristic (ROC) curve was constructed to assess the prognostic ability. We estimated area under ROC curve (AUC) and 95% CI. We considered a $P < 0.05$ as statistical significant differences. Statistical analyses were completed using SPSS 190.

## 3. Results

### 3.1. Study population characteristics

Initially, a total of 148 sTBI patients were recruited. 46 patients were further excluded because of age < 18 y (3 patients), pregnancy (2 patients), inflammatory or malignant disease (5 patients), use of antiplatelet or anticoagulant medication (6 patients), previous intracerebral hemorrhage or subarachnoid hemorrhage (8 patients), injury severity score in non-cranial aspects > 9 points (10 patients) and time from trauma to admission > 6 h (12 patients). Ultimately, 102 patients were included in this study. Alternatively, 102 controls of similar age and gender percentage were enrolled.

This group of sTBI patients had a median age of 45 y (range, 18–76 y; the upper - lower quartiles, 34–61 y), among whom there were 65 males and 37 females. With respect to traumatic cause, 52 patients suffered from automobile/motorcycle, 39 patients experienced fall/jump and 11 patients were traumatized on account of others. The positive trauma-related cerebral lesions included skull-cap fracture in 74 patients, skull-base fracture 58 patients, epidural hematoma in 46 patients, subdural hematoma in 79 patients, traumatic subarachnoid hemorrhage in 87 patients, cerebral hematoma in 76 patients, brain contusion in 65 patients and pneumocephalus in 44 patients. The patients were admitted at a median value of 2.2 h post-injury (the upper - lower quartiles, 1.7–2.8 h; range, 0.5–6.0 h). Trauma severity was assessed using GCS score, whose median value was 5 (the upper - lower quartiles, 4–7; range, 3–8). Among all patients, 62 had GCS scores 3–5 and 40 showed GCS scores 6–8. We observed pupillary reaction and found that pupils of 45 patients (44.1%) were unreactive. The initial CT scans showed that 43 patients (42.2%) had CT classification 5 or 6; 46 patients (45.1%), abnormal cisterns; 54 patients (52.9%), midline shift > 5 mm. In addition, the median systolic arterial pressure was 120 mmHg (range, 70–172 mmHg; the upper - lower quartiles, 94–160 mmHg) and the median diastolic arterial pressure was 70 mmHg (the upper - lower quartiles, 54–90 mmHg; rang, 40–110 mmHg). Blood samples were collected from 0.8 to 7.7 h post-trauma (median, 3.2 h; the upper - lower quartiles, 2.7–3.6 h). Laboratory test showed that blood glucose concentrations ranged from 2.9 to 18.6 mmo/lL, with a median value of 9.5 mmol/L(the upper - lower quartiles, 7.5–11.1 mmo/lL); blood white blood cell count ranged from 4.0 to 13.1 × $10^9$/L, with a median value of 7.7 × $10^9$/L (the upper - lower quartiles, 5.7–9.2 × $10^9$/L).

### 3.2. Serum SPARCL1 concentrations

As compared to the controls, the patients exhibited substantially higher serum SPARCL1 concentrations (Fig. 1). As regards to its correlation with trauma severity among the sTBI patients, we identified GCS score as the continuous or categorical variable, and thereby, in

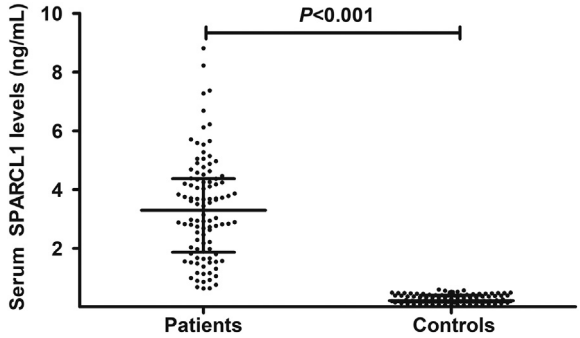


**Fig. 1.** Comparison of serum secreted protein acidic and rich in cysteine-like 1 (SPARCL1) levels between controls and patients with severe traumatic brain injury.

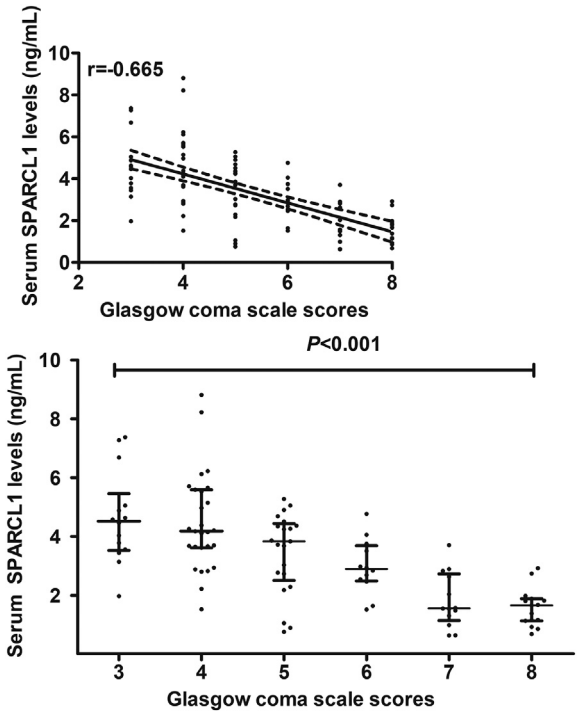


**Fig. 2.** Association of Glasgow coma scale scores with serum secreted protein acidic and rich in cysteine-like 1 (SPARCL1) levels with SPARCL1 level identified as a continuous or categorical variable.

**Table 1**
The variables correlated with serum secreted protein acidic and rich in cysteine-like 1 levels after traumatic brain injury using bivariate correlation analysis.

| | r value | *P* value |
|---|---|---|
| Gender (male/female) | 0.089 | NS |
| Age (y) | 0.078 | NS |
| Traumatic cause | 0.102 | NS |
| Glasgow Coma Scale score | −0.665 | < 0.001 |
| Unreactive pupils | 0.391 | < 0.001 |
| Marshall CT classification 5 or 6 | 0.295 | 0.003 |
| Abnormal cisterns | 0.211 | NS |
| Midline shift > 5 mm | 0.213 | 0.032 |
| Admission time (h) | 0.028 | NS |
| Blood-collecting time (h) | 0.048 | NS |
| Systolic arterial pressure (mmHg) | 0.174 | NS |
| Diastolic arterial pressure (mmHg) | 0.129 | NS |
| Blood glucose levels (mmol/L) | 0.318 | 0.001 |
| Blood white blood cell count ($\times 10^9$/L) | 0.035 | NS |

APACHE II indicates Acute Physiology and Chronic Health Evaluation II; CT, computerized tomography.

Fig. 2, serum SPARCL1 concentrations were revealed to be strongly raised with increasing severity of brain injury indicated by decreasing GCS score. In Table 1, via bivariate correlation analysis, we revealed that serum SPARCL1 concentrations were intimately correlated with GCS score, unreactive pupils, Marshall CT classification 5 or 6, abnormal cisterns, midline shift > 5 mm and blood glucose concentrations. Moreover, using a multivariate linear regression model including the preceding significant variables, it was found that serum SPARCL1 concentrations were independently related to GCS score ($t = -7.011$, $P < 0.001$).

In Fig. 3, patients with GCS scores 3–5 had substantially higher serum SPARCL1 concentrations that those with GCS scores 6–8. In addition, we conFig.d a ROC curve. Serum SPARCL1 concentrations significantly differentiated between GCS scores 3–5 and GCS scores 6–8 (AUC, 0.867; 95% CI, 0.785–0.926); also, an optimal cutoff value of

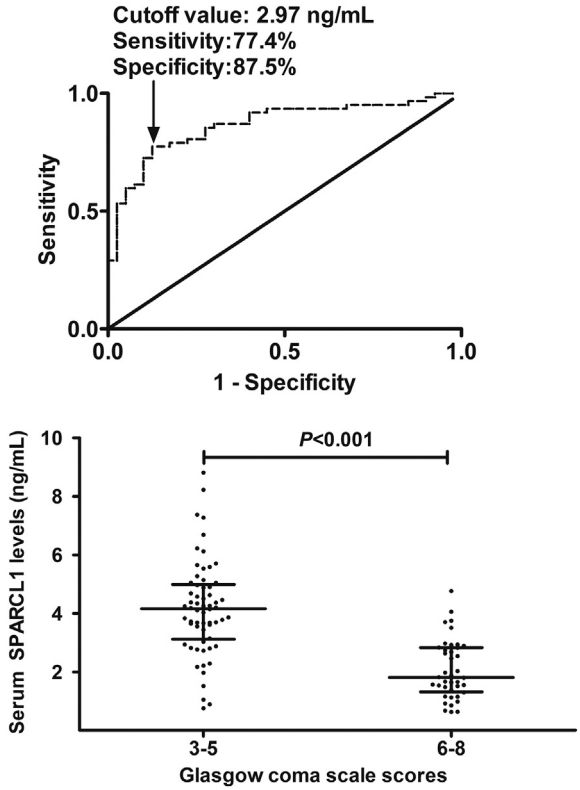


**Fig. 3.** Comparison of serum secreted protein acidic and rich in cysteine-like 1 (SPARCL1) levels between severe traumatic brain injury patients with Glasgow coma scale scores 3–5 and 6–8, as well as discriminatory ability of serum SPARCL1 levels for Glasgow coma scale scores 3–5 according to receiver operating characteristic curve.

serum SPARCL1 concentrations was chosen to discriminate GCS scores 3–5, which yielded the corresponding sensitivity and specificity values (Youden index J = 0.649). Moreover, all patients were dichotomized in accordance with the median value of serum SPARCL1 concentrations (3.29 ng/mL). Just as listed in Table 2, using univariate logistic regression analysis, we demonstrated that serum SPARCL1 concentrations > 3.29 ng/mL were markedly associated with GCS score, unreactive pupils, Marshall CT classification 5 or 6, abnormal cisterns and midline shift > 5 mm. Further, the aforementioned significant parameters were incorporated into the binary logistic regression model and

**Table 2**
The parameters associated with serum secreted protein acidic and rich in cysteine-like 1 levels > 3.29 ng/mL following traumatic brain injury using univariate binary logistic regression analysis.

| | Odds ratio | 95% CI | *P* value |
|---|---|---|---|
| Gender (male/female) | 0.775 | 0.345–1.741 | NS |
| Age (y) | 1.011 | 0.987–1.035 | NS |
| Traumatic cause | 1.480 | 0.823–2.661 | NS |
| Glasgow Coma Scale score | 0.324 | 0.212–0.495 | < 0.001 |
| Unreactive pupils | 7.273 | 3.000–17.632 | < 0.001 |
| Marshall CT classification 5 or 6 | 3.484 | 1.522–7.972 | 0.003 |
| Abnormal cisterns | 2.232 | 1.007–4.949 | 0.048 |
| Midline shift > 5 mm | 3.100 | 1.380–6.964 | 0.006 |
| Admission time (h) | 0.943 | 0.674–1.320 | NS |
| Blood-collecting time (h) | 1.041 | 0.767–1.414 | NS |
| Systolic arterial pressure (mmHg) | 0.990 | 0.977–1.004 | NS |
| Diastolic arterial pressure (mmHg) | 0.993 | 0.973–1.013 | NS |
| Blood glucose levels (mmol/L) | 1.072 | 0.964–1.192 | NS |
| Blood white blood cell count L($\times 10^9$/L) | 0.993 | 0.840–1.175 | NS |

APACHE II denotes Acute Physiology and Chronic Health Evaluation II; CT, computerized tomography.

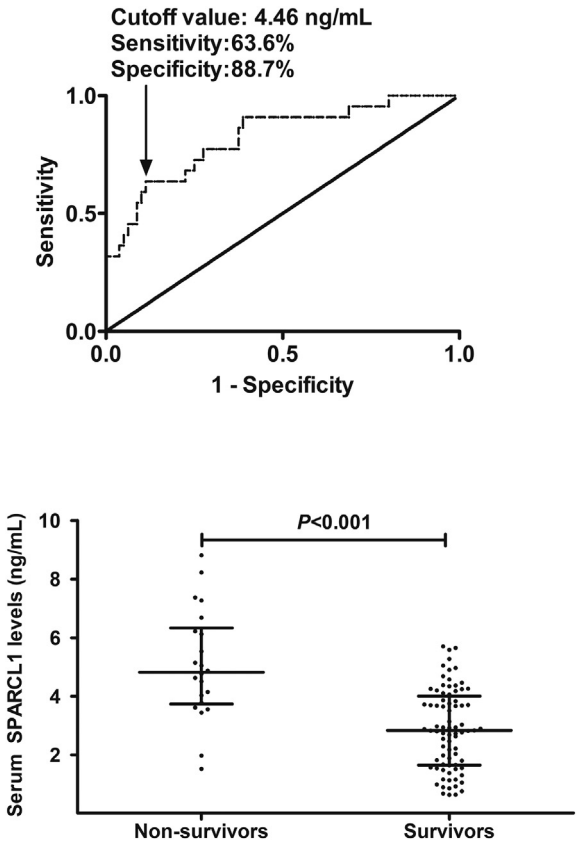


**Fig. 4.** Comparison of serum secreted protein acidic and rich in cysteine-like 1 (SPARCL1) levels between severe traumatic brain injury patients dying and alive during hospital stay, as well as discriminatory ability of serum SPARCL1 levels for in-hospital mortality in accordance with receiver operating characteristic curve.

afterwards, it was verified that GCS score had independent relation to serum SPARCL1 concentrations > 3.29 ng/mL with OR value of 0.341 (95% CI, 0.218–0.533).

### 3.3. In-hospital mortality prediction

In-hospital mortality was 21.6% (22/102). In order to determine whether serum SPARCL1 concentrations could statistically significantly distinguish patients at risk of death during hospital stay after trauma, we conFig.d a ROC curve. In Fig. 4, compared with survivors, serum SPARCL1 concentrations were substantially increased in non-survivors; additionally, serum SPARCL1 concentrations had 0.822 at AUC (95% CI, 0.734–0.891). Meantime, an optimal cutoff value (4.46 ng/mL) was selected, which predicted in-hospital mortality with 63.6% sensitivity and 88.7% specificity (Youden J index = 0.524).

Table 3 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 serum SPARCL1 concentrations > 3.29 ng/mL, as well as higher blood glucose concentrations were pronouncedly associated with higher risk of death during hospital stay following trauma. Moreover, the above-mentioned significant variables were entered into the binary logistic regression model and subsequently, serum SPARCL1 concentrations > 3.29 ng/mL (OR = 10.052, 95% CI = 1.918–52.686, $P = 0.006$) and GCS score (OR = 0.168, 95% CI = 0.056–0.504, $P = 0.001$) emerged as the two independent predictors for in-hospital mortality after head trauma.

**Table 3**
The factors related to in-hospital mortality following traumatic brain injury utilizing univariate binary regression analysis.

| | Odds ratio | 95% CI | *P* value |
|---|---|---|---|
| Gender (male/female) | 1.286 | 0.471–3.512 | NS |
| Age (y) | 1.032 | 1.001–1.064 | 0.043 |
| Traumatic cause | 1.417 | 0.719–2.793 | NS |
| Glasgow Coma Scale score | 0.182 | 0.080–0.415 | < 0.001 |
| Unreactive pupils | 22.000 | 4.771–101.447 | < 0.001 |
| Marshall CT classification 5 or 6 | 3.980 | 1.452–10.904 | 0.007 |
| Abnormal cisterns | 4.444 | 1.568–12.596 | 0.005 |
| Midline shift > 5 mm | 5.500 | 1.708–17.713 | 0.004 |
| Admission time (h) | 0.915 | 0.595–1.407 | NS |
| Blood-collecting time (h) | 0.960 | 0.657–1.403 | NS |
| Systolic arterial pressure (mmHg) | 1.000 | 0.983–1.016 | NS |
| Diastolic arterial pressure (mmHg) | 1.008 | 0.985–1.033 | NS |
| Blood glucose levels (mmol/L) | 1.179 | 1.027–1.354 | 0.020 |
| Blood white blood cell count ($\times 10^9$/L) | 1.056 | 0.862–1.292 | NS |
| Serum SPARCL1 levels > 3.29 ng/mL | 15.806 | 3.452–72.383 | < 0.001 |

CT, computerized tomography; APACHE II, Acute Physiology and Chronic Health Evaluation II; SPARCL1, secreted protein acidic and rich in cysteine-like 1.

## 4. Discussion

At first, compared with the controls, sTBI patients exhibited significant increases of serum SPARCL1 concentrations. Secondly, serum SPARCL1 concentrations were inversely correlated with GCS scores among sTBI patients. Thirdly, both serum SPARCL1 and GCS score were the independent predictors for in-hospital mortality. At last, serum SPARCL1 showed a high discriminatory ability for patients at risk of death during hospital stay in this group of sTBI patients. In summary, those accumulating evidence implies that serum SPARCL1 might serve as a promising prognostic biomarker among sTBI patients.

SPARCL1 is an antiadhesive glycoprotein that belongs to the extracellular proteins that regulate cell–matrix interactions and thus is implicated in tissue remodeling [15–17]. As in several types of cancer, the expression of SPARCL1 was lowered and subsequently it was speculated that it may be a tumor suppressor factor [23–27]. Matricellular proteins in the brain are pivotal in developmental processes, and they also play an essential role in the support of neuronal integrity [11–14]. SPARCL1 is a member of family of extracellular matrix molecules. It can influence synaptic stability and is upregulated during axonal regeneration after brain injury [19]. In healthy brains, the mRNA coding this protein is expressed by most of the cells, while astrocytes have higher expression concentrations of SPARCL1 mRNA than any other cell type [28]. Previous animal studies have confirmed that SPARCL1 is upregulated in astrocytes after transient ischemia [29]. Moreover, SPARCL1 staining was prominently observed in the injured white-matter tracts within the infarct zone of animals with ischemic stroke [20]. The preceding accumulating evidence hints that SPARCL1 might be involved in brain injury after some neurological diseases, such as TBI.

In 2017, a report showed that serum SPARCL1 concentrations were positively correlated with NIHSS scores; as compared to patients with NIHSS scores < 5 at admission, patients with moderate and severe stroke (NIHSS scores ≥6) had apparently higher SPARCL1 concentrations; SPARCL1 appeared as an independent predictor for stroke severity at admission; thus, it comes into conclusion that SPARCL1 concentrations are independently associated with ischemic stroke severity evaluated by the NIHSS scores [21]. In the current study, GCS scores were utilized to assess clinical severity of brain trauma. Five statistical methods, including univariate and multivariate analyses as well as with serum SPARCL1 concentrations identified as the continuous and categorical variables, were done to analysis the relationship between serum SPARCL1 concentrations and trauma severity as reflected by GCS scores. It was verified that serum SPARCL1 concentrations were

inversely correlated with GCS scores, implying that serum SPARCL1 concentrations could reflect trauma severity of TBI.

Up to now, no studies have reported the relation of serum SPARCL1 concentrations to prognosis of acute brain injury diseases. Our study selected in-hospital mortality as a prognostic parameter and further evaluated its association with serum SPARCL1 concentrations. After some factors were screened using bivariate analysis, a multivariate logistic regression model, including the preceding significant variables, was constructed. Thereby, we found, besides GCS score, serum SPARCL1 were an independent predictor for in-hospital mortality. Still, a ROC curve was conFig.d and further we revealed a high predictive value of serum SPARCL1 concentrations for in-hospital mortality. Such finding was supportive of the notion that serum SPARCL1 concentrations might be closely associated with clinical outcome.

## 5. Conclusions

Based on our data, we cautiously assert that serum SPARCL1 concentrations rising after sTBI are independently associated with trauma severity assessed by the GCS scores and short-term mortality reflected by in-hospital mortality, indicating serum SPARCL1 might represent a useful biomarker for reflecting prognosis of head trauma.

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