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Serum soluble TWEAK levels in severe traumatic brain injury and its prognostic significance

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ABSTRACT

Background: Severe traumatic brain injury (sTBI) is characterized by a high mortality. Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) participates in inflammation. We determined serum soluble TWEAK (sTWEAK) levels with respect to its prognostic ability.

Methods: This was a single-center prospective, observational study that was performed from December 2014 to December 2017. A total of 114 sTBI patients who met the inclusion criteria and 114 randomly selected healthy controls were included in the study. Serum sTWEAK levels were gauged. Patients were followed-up until death or completion of 6 months. Poor outcome was referred to as Glasgow outcome scale score of 1–3.

Results: In comparison with controls, patients displayed predominantly higher serum sTWEAK levels. Serum sTWEAK levels were strongly correlated with Glasgow coma scale scores and serum C-reactive protein levels. 32 patients (28.1%) died and 60 patients (52.6%) suffered from a poor outcome. Receiver operating characteristic curve analysis clearly showed that serum sTWEAK levels had substantially high predictive performance for 6-month mortality and poor outcome. Serum sTWEAK emerged as an independent predictor for 6-month mortality, overall survival and poor outcome.

Conclusions: Raised serum sTWEAK levels are closely related to increasing inflammatory response, elevated trauma severity and worse clinical outcome after sTBI.

1. Introduction

Traumatic brain injury (TBI) is a very frequent cause of emergency department visits in adult populations [1–3]. Severe TBI (sTBI) is one of the leading causes of death and morbidity in adults [1–3]. Neuroinflammation is initially described as an accumulation of leukocytes in brain. Gradually, it is known that neuroinflammation results from peripheral immune cell infiltration through the brain barriers, from cytokine secretion and from oxidative stress. Also, resident central nervous system cells such as astrocytes and microglia are involved in regulating neuroinflammation and respond to central nervous system insults by a proliferation and an abnormal activation, respectively called astrogliosis and microgliosis [4–8]. Undoubtedly, neuroinflammation is an important aspect implicated in mechanisms underlying traumatic secondary brain injury [9–11].

Tumor necrosis factor-like weak inducer of apoptosis (TWEAK), a member of tumor necrosis factor superfamily, is initially revealed to induce apoptosis of malignant cells [12–14]. TWEAK can act as an inflammatory cytokine via binding to fibroblast growth factor inducible 14 (Fn14), a member of the tumor necrosis factor receptor superfamily [15–17]. Fn14 can be highly inducible in endothelial cells, neurons, astrocytes, microglia, and progenitor cells under some pathological conditions [15–17]. TWEAK interaction with its Fn14 receptor activates nuclear factor-κB and mitogen-activated protein kinase signaling pathways [18–20]. Admittedly, TWEAK contributes to inflammation response. In the central nervous system, TWEAK targets endothelial cells, astrocytes and neurons [15–17]. Accumulating evidence shows that TWEAK participates in neuroinflammation [15–17]. TWEAK included two forms, namely transmembrane protein and soluble cytokine (sTWEAK). sTWEAK can be released greatly from monocytes, macrophages, astrocytes and microglia in inflammatory tissues [21–23]. A previous study has shown that serum sTWEAK levels were pronouncedly enhanced in patients with ischemic stroke [24]. However, they have not been explored in sTBI patients. Thus, the aim of this study was

Abbreviations: GCS, Glasgow coma scale; GOS, Glasgow outcome scale; sTBI, severe traumatic brain injury; sTWEAK, soluble tumor necrosis factor-like weak inducer of apoptosis

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to investigate the link between serum sTWEAK levels and inflammatory reaction, trauma severity and prognosis in a group of sTBI patients.

2. Materials and methods

2.1. Subjects

This prospective observational study was conducted in the First People's Hospital of Jiande City, Jiande City, China. Here, we included patients admitted from December 2014 to December 2017. The investigation was conducted in compliance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol followed in this study was approved by the Institutional Review Board at our hospital and the written informed consent was obtained from subject legal guardians. We initially assessed adult patients with isolated and blunt sTBI (age ≥ 18 years, Glasgow Coma Scale (GCS) score ≤ 8 points and injury severity score in non-cranial aspects < 9 points) who arrived at our emergency room within 6 h following trauma. We excluded patients with inflammatory, immunological, hematological or malignant disease, use of antiplatelet or anticoagulant medication or previous neurological diseases such as head trauma, intracerebral hemorrhage and subarachnoid hemorrhage. Simultaneously, controls enrolled in this study were composed of volunteers free of other diseases based on medical history, physical examination and biochemical test.

2.2. Data recorded

In the current study, the collected variables mainly included demographics, nature of trauma, vital signs and laboratory parameters. Demographics contained age, gender and body mass index. Laboratory parameters included leukocytes, glycemia, platelets and C-reactive protein. Vital signs were composed of arterial blood pressure, respiratory rate and heart rate. Nature of trauma comprised admission time after trauma, GCS score for reflecting trauma severity, pupillary reactivity for assessing brain stem function, trauma cause (automobile/motorcycle, fall/jump or others) and radiological parameters detected using emergency head computerized tomography (CT) scan. Those radiological parameters included midline shift, abnormal cisterns, the Marshall CT classification and types of craniocerebral injury, namely, skull-cap fracture, skull-base fracture, epidural hematoma, subdural hematoma, traumatic subarachnoid hemorrhage, cerebral hematoma, brain contusion and pneumocephalus. All patients were followed up until death or completion of post-trauma 6 months. Function outcome were assessed using Glasgow outcome scale (GOS), which is composed of 5 grades. Poor outcome was designated as GOS score of 1–3. Subsequently, 6-month mortality, overall survival and poor outcome constituted study endpoints in this study.

2.3. Immune analysis

Blood samples of patients and controls were drawn by venous puncture at admission and at study entrance respectively. After blood centrifugation, serum samples were collected, aliquoted and promptly stored at −80 °C until assay. When blood samples were collected, serum C-reactive protein concentrations, leukocytes, glycemia and platelets were measured. Every 3 months, serum sTWEAK levels were quantified in duplicates using a commercial enzyme-linked immunosorbent assay kit bought from Bender Medsystems (Vienna, Austria), as per the manufacturer's protocol.

2.4. Statistical analysis

The softwares used for this statistical assessment were GraphPad PRISM 7.0.a and SPSS ver 19.0. Medians and interquartile ranges were used to report quantitative variables, as well as frequencies and percentages to report qualitative variables. A non-parametric Wilcoxon-Mann-Whitney test or Kruskal-Wallis H test was carried out to compare quantitative variables between groups, and χ^2 test or Fisher's exact test to compare qualitative variables. Spearman's rank correlation coefficient was utilized to test the correlation between sTWEAK serum levels and other variables. Receiver operating characteristic (ROC) analysis was performed to estimate the sensitivity and specificity of sTWEAK serum levels to distinguish non-survivors from survivors or to differentiate between patients with poor outcome and good outcome. Overall survival was estimated using the Kaplan–Meier method. Intergroup comparison of survival time was done using the log-rank test. A multivariate binary logistic regression model or multivariate Cox's proportional hazard model was conFig.d to identify variables independently associated with 6-month mortality or overall survival. A $p < .05$ was considered statistically significant.

3. Results

3.1. Study population characteristics

During the study period, we initially assessed a total of 148 adult patients suffering from isolated and blunt sTBI and admitted to the emergency room within 6 hours post trauma. Next, in accordance with the exclusion criteria, we excluded 12 patients with inflammatory, immunological, hematological or malignant disease, 10 with use of antiplatelet or anticoagulant medication and 8 with previous neurological diseases, such as head trauma, intracerebral hemorrhage and subarachnoid hemorrhage. In addition, 4 patients lost to follow-up. Finally, a total of 114 patients were evaluated in the current study. Likewise, one hundred and fourteen controls were enrolled. By comparison, there were not remarkable differences in terms of age, gender and body mass index between the patients and the controls.

The included patients, with 68 males and 46 females, were aged from 18 to 75 y (median, 45 years; the upper - lower quartiles, 31–60 y) and their median body mass index was 23.5 kg/m^2 (range, 18.1–27.9 kg/m^2; the upper - lower quartiles, 22.6–26.2 kg/m^2). The median systolic arterial pressure and diastolic arterial pressure were 119 mmHg (range, 72–170 mmHg; the upper - lower quartiles, 93–135 mmHg) and 72 mmHg (rang, 45–112 mmHg; the upper - lower quartiles, 55–91 mmHg) respectively. Respiratory rate ranged from 4 to 26/min (median, 13/min; the upper - lower quartiles, 10–17/min) and heart rate ranged from 24 to 97/min (median, 53/min; the upper - lower quartiles, 40–72/min). Trauma causes included automobile/motorcycle (53 patients), fall/jump (45 patients) and others (16 patients). Head CT examination displayed skull-cap fracture in 76 patients, skull-base fracture in 55 patients, epidural hematoma in 48 patients, subdural hematoma in 74 patients, traumatic subarachnoid hemorrhage in 89 patients, cerebral hematoma in 73 patients, brain contusion in 64 patients and pneumocephalus in 43 patients. The patients were admitted to the emergency room from 0.5 to 6.0 h after head trauma (media, 2.1 h; the upper - lower quartiles, 1.6–2.6 h). GCS scores ranged from 3 to 8 (median, 5; the upper - lower quartiles, 4–6). There were GCS score 3 in 17 patients, score 4 in 24, score 5 in 28, score 6 in 20, score 7 in 10 and score 8 in 15. There were 49 patients (43.0%) with unreactive pupils. CT classification 5 or 6 was identified in 48 patients (42.1%). Abnormal cisterns were shown among 55 patients (48.2%). Midline shift > 5 mm was revealed for 64 patients (56.1%). A total of 70 patients (61.4%) underwent a surgery in the first 24 h after head trauma. We collected blood samples from 1.1 to 7.9 h post trauma (median, 3.1 h; the upper - lower quartiles, 2.8–3.7 h). In total, 32 patients (28.1%) were dead within 6 months after head trauma and sixty patients (52.6%) experienced a poor outcome at post-traumatic 6 months. In addition, there were 32 patients with GOS score 1, 15 with GOS score 2, 13 with GOS score 3, 39 with GOS score 4 and 15 with GOS score 5.

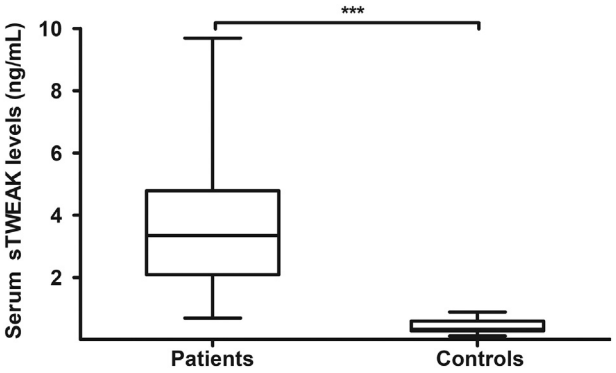

Fig. 1. Difference in serum sTWEAK levels between controls and patients with severe traumatic brain injury. sTWEAK denotes soluble tumor necrosis factor-like weak inducer of apoptosis. $^{***}P < .001$.

3.2. Serum sTWEAK levels and other variables

In this part, we found that patients tended to display predominantly elevated serum sTWEAK levels, as opposed to controls (Fig. 1). Alternatively, among this group of patients, serum sTWEAK levels were overtly raised with rising serum C-reactive protein levels (Fig. 2) and also with decreasing GCS scores (Fig. 3). Simultaneously, patients with higher grade of GOS exhibited pronouncedly lower serum sTWEAK levels (Fig. 4). Also, non-survivors within 6 months post trauma had substantially higher serum sTWEAK levels than survivors (Fig. 5); and serum sTWEAK levels were significantly enhanced in patients at risk of 6-month unfavorable outcome than in those with favorable outcome (Fig. 5).

3.3. Serum sTWEAK levels and clinical outcomes

As depicted in Fig. 6, serum sTWEAK levels statistically significantly discriminated patients at risk of 6-month mortality and unfavorable outcome with areas under curve of 0.806 (95% CI, 0.721–0.874) and 0.841 (95% CI, 0.761–0.903) respectively. In addition, 2 optimal cutoff value were chosen, which yielded the corresponding sensitivity and specificity values (Youden J index = 0.503 and 0.546 respectively; Fig. 6). Meanwhile, serum sTWEAK levels were dichotomized according to its median value (3.35 ng/ml) and subsequently, it was revealed that patients with serum sTWEAK levels ≥3.35 ng/ml had substantially shorter overall survival time than those who presented with serum sTWEAK levels < 3.35 ng/ml (Fig. 7).

As listed in Table 1, univariate analyses showed that variables

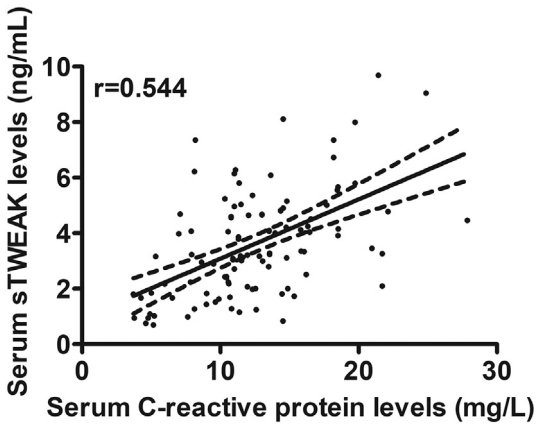

Fig. 2. Relation of serum sTWEAK levels with serum C-reaction protein levels in patients with severe traumatic brain injury. sTWEAK denotes soluble tumor necrosis factor-like weak inducer of apoptosis.

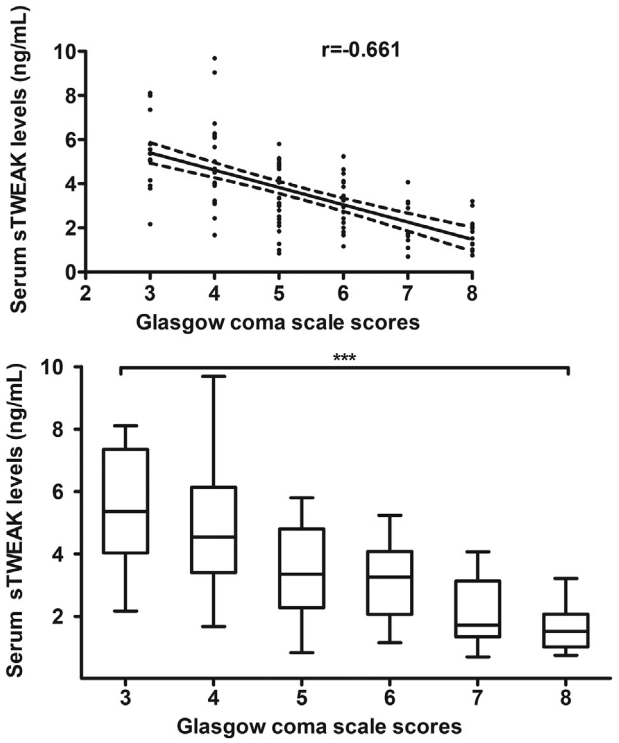

Fig. 3. Relationship between serum sTWEAK levels and Glasgow coma scale scores among patients with severe traumatic brain injury. sTWEAK denotes soluble tumor necrosis factor-like weak inducer of apoptosis. $^{***}P < .001$.

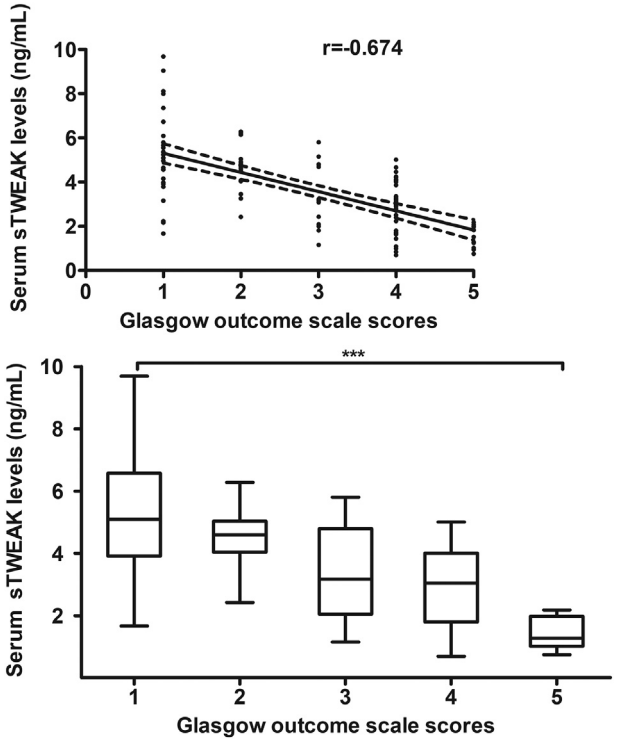

Fig. 4. Association of serum sTWEAK levels with Glasgow outcome scale scores among severe traumatic brain injury patients. sTWEAK denotes soluble tumor necrosis factor-like weak inducer of apoptosis. $^{***}P < .001$.

robustly associated with 6-month mortality, overall survival and unfavorable outcome were GCS scores, age, presence of unreactive pupils, CT classification 5 or 6, abnormal cisterns, midline shift > 5 mm, blood

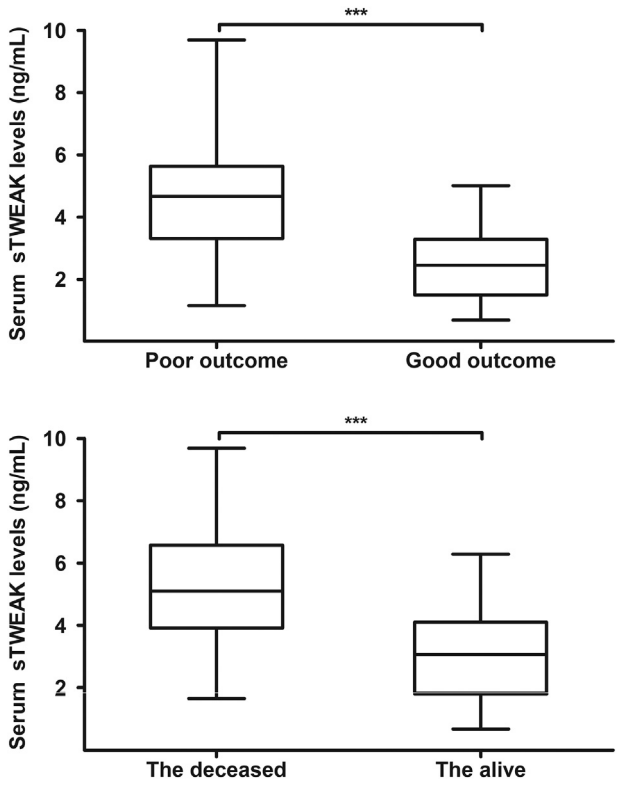

Fig. 5. Comparisons of serum sTWEAK levels between non-survivor and survivors within six months after head trauma as well as between patients with poor outcome and those with good outcome at six months post trauma. sTWEAK denotes soluble tumor necrosis factor-like weak inducer of apoptosis. $^{***}P < .001$.

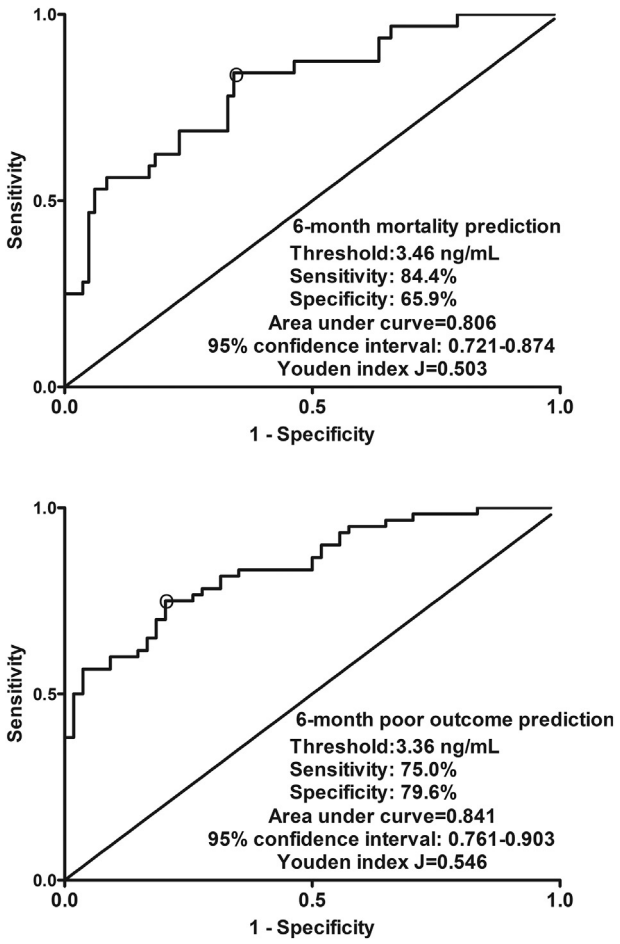

Fig. 6. Receiver operating characteristic curve analysis of serum levels of soluble tumor necrosis factor-like weak inducer of apoptosis for predicting 6-month mortality and poor outcome after severe traumatic brain injury.

glucose levels, serum C-reactive protein levels and serum sTWEAK levels. In order to identify the independent predictors for the aforementioned poor prognoses, we incorporated the preceding significant variables in univariate analyses to the multivariate models and thereby found that serum sTWEAK levels, presence of unreactive pupils and GCS scores retained as the independent predictors for 6-month mortality, overall survival and unfavorable outcome (Table 2).

4. Discussion

Although a previous report has determined serum sTWEAK levels and found its significant elevation in patients with acute ischemic stroke, in comparison to healthy control [24], there is a paucity of data available on serum sTWEAK levels after head trauma. In the current study, we revealed that (1) serum sTWEAK levels were substantially higher in sTBI patients than in healthy volunteers; (2) serum sTWEAK levels were intimately correlated with serum C-reactive protein levels, GCS scores and GOS scores; (3) serum sTWEAK levels were remarkably elevated in sTBI patients dying within 6 months or presenting with a poor outcome at 6 months following trauma, as opposed to the remainders; (4) serum sTWEAK and other variables, including GCS scores and unreactive pupils, emerged as the three independent predictors for long-term prognoses, namely 6-month mortality, overall survival and poor outcome; and (5) serum sTWEAK levels displayed a considerably high discriminatory capability for 6-month mortality, overall survival or poor outcome under ROC curve. Given the preceding data, it is assumed that serum sTWEAK might be in close association with trauma severity, inflammatory response and long-term clinical outcomes after head trauma.

sTBI is a common form of trauma globally and is also a type of disease with high incidence, mortality and disability rate worldwide. In

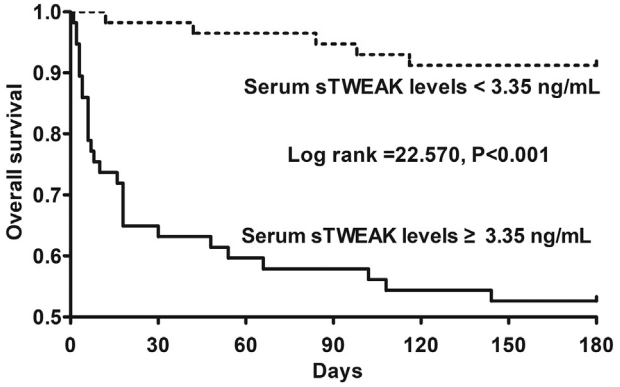

Fig. 7. Overall survival curve based on serum sTWEAK levels in patients with severe traumatic brain injury. All patients were grouped according to the median value of serum sTWEAK levels (3.35 ng/ml). sTWEAK denotes soluble tumor necrosis factor-like weak inducer of apoptosis.

general, approximately 30% of sTBI patients will die within 6 months following head trauma and almost 50% of survivors will be permanently disabled [25–27]. Therefore, it causes a tremendous burden on health resources. In the current study, posttraumatic six-month mortality was 28.1% and 52.6% patients suffered from a poor outcome (GOS score 1–3) at 6 months post trauma. Such poor prognoses were similar to the previously reported data [25–27]. A poor outcome is very commonly defined as GCS score of 1–3 [28,29], which was also used in

Table 1
The factors associated with 6-month poor prognoses after severe traumatic brain injury.

	6-month mortality		6-month unfavorable outcome		6-month overall survival	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender (male/female)	1.422 (0.607–3.328)	NS	1.031 (0.487–2.182)	NS	1.392 (0.671–2.888)	NS
Age (y)	1.034 (1.006–1.063)	0.019	1.030 (1.006–1.055)	0.014	1.029 (1.005–1.053)	0.019
Body mass index (kg/m^2)	1.181 (0.985–1.415)	NS	1.128 (0.968–1.315)	NS	1.108 (0.957–1.281)	NS
Traumatic causes	1.723 (0.970–3.062)	NS	1.594 (0.932–2.729)	NS	1.548 (0.962–2.490)	NS
GCS score at admission	0.212 (0.114–0.392)	< 0.001	0.234 (0.139–0.396)	< 0.001	0.290 (0.192–0.439)	< 0.001
Presence of unreactive pupils	8.631 (3.293–22.625)	< 0.001	5.630 (2.465–12.862	< 0.001	6.173 (2.661–14.319)	< 0.001
Marshall CT classification 5 or 6	2.671 (1.155–6.176)	0.022	3.736 (1.688–8.269)	0.001	2.234 (1.102–4.530)	0.026
Initial abnormal cisterns	3.993 (1.641–9.716)	0.002	3.217 (1.492–6.940)	0.003	3.231 (1.493–6.990)	0.003
Midline shift > 5 mm at baseline	5.018 (1.868–13.478)	0.001	6.571 (2.884–14.972)	0.001	4.173 (1.716–10.151)	0.002
Admission time (h)	0.907 (0.616–1.336)	NS	0.901 (0.646–1.257)	NS	0.935 (0.681–1.285)	NS
Blood-sampling time (h)	0.918 (0.649–1.299)	NS	0.930 (0.688–1.258)	NS	0.934 (0.703–1.240)	NS
Surgery in the first 24 h	0.620 (0.271–1.421)	NS	1.187 (0.558–2.527)	NS	0.712 (0.355–1.426)	NS
Systolic arterial pressure (mmHg)	0.998 (0.984–1.013)	NS	0.991 (0.978–1.004)	NS	0.998 (0.986–1.011)	NS
Diastolic arterial pressure (mmHg)	1.007 (0.986–1.028)	NS	0.998 (0.979–1.017)	NS	1.006 (0.989–1.024)	NS
Heart rate (/min)	0.997 (0.979–1.016)	NS	0.994 (0.978–1.011)	NS	0.997 (0.982–1.013)	NS
Respiratory rate (/min)	0.928 (0.851–1.012)	NS	0.995 (0.910–1.088)	NS	0.949 (0.878–1.026)	NS
Blood glucose levels (mmol/l)	1.197 (1.063–1.347)	0.003	1.201 (1.075–1.342)	0.001	1.173 (1.067–1.290)	0.001
Blood WBC count ($\times 10^9$/l)	1.097 (0.930–1.293)	NS	0.982 (0.846–1.140)	NS	1.119 (0.960–1.305)	NS
Blood platelet count ($\times 10^9$/l)	0.990 (0.980–1.001)	NS	0.995 (0.986–1.003)	NS	0.991 (0.982–1.001)	NS
Serum CRP levels (mg/l)	1.103 (1.009–1.206)	0.030	1.138 (1.042–1.243)	0.004	1.080 (1.010–1.155)	0.025
Serum sTWEAK levels (ng/ml)	2.155 (1.549–2.998)	< 0.001	2.615 (1.818–3.761)	< 0.001	1.571(1.346–1.834)	< 0.001

Odds ratio (OR), hazard ratio (HR) and the corresponding 95% confidence interval (CI) values were estimated using univariate binary logistic regression analysis or Cox's proportional hazard analysis as appropriate. CT means computerized tomography; GCS, Glasgow coma scale; WBC, white blood cell; sTWEAK, soluble tumor necrosis factor-like weak inducer of apoptosis; CRP, C-reactive protein.

Table 2
The factors in independent association with 6-month poor prognoses following severe traumatic brain injury.

	6-month mortality		6-month unfavorable outcome		6-month overall survival	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (y)	1.023 (0.977–1.071)	NS	1.024 (0.979–1.072)	NS	1.010 (0.980–1.040)	NS
GCS score at admission	0.324 (0.160–0.656)	0.002	0.337 (0.172–0.661)	0.002	0.375 (0.217–0.649)	< 0.001
Presence of unreactive pupils	9.869 (2.013–48.370)	0.005	17.652 (2.252–138.356)	0.006	7.229 (2.356–22.181)	0.001
Marshall CT classification 5 or 6	1.158 (0.086–11.534)	NS	1.509 (0.072–31.470)	NS	1.218 (0.067–14.707)	NS
Initial abnormal cisterns	1.558 (0.181–13.409)	NS	1.116 (0.076–8.401)	NS	1.140 (0.282–4.612)	NS
Midline shift > 5 mm at baseline	1.446 (0.206–10.174)	NS	4.254 (0.653–27.694)	NS	1.608 (0.392–6.586)	NS
Blood glucose levels (mmol/l)	0.936 (0.793–1.105)	NS	1.213 (0.995–1.478)	NS	0.925 (0.833–1.028)	NS
Serum CRP levels (mg/l)	0.976 (0.842–1.132)	NS	1.030 (0.895–1.185)	NS	1.007 (0.918–1.106)	NS
Serum sTWEAK levels (ng/ml)	1.668 (1.021–2.724)	0.041	1.824 (1.040–3.198)	0.036	1.284(1.010–1.677)	0.046

Odds ratio (OR), hazard ratio (HR) and the corresponding 95% confidence interval (CI) values were estimated using multivarite binary logistic regression analysis or Cox's proportional hazard analysis as appropriate. CT means computerized tomography; GCS, Glasgow coma scale; WBC, white blood cell; sTWEAK, soluble tumor necrosis factor-like weak inducer of apoptosis; CRP, C-reactive protein.

this study. A growing body of data has shown that GCS score and sometimes unreactive pupils are independently associated with prognosis after head trauma [30,31], which were verified in this study. Taken together, the above-mentioned analyses showed that our data could possess statistical power.

TWEAK belongs to the tumor necrosis factor family and functions via binding to the membrane receptor Fn14, which is a member of the tumor necrosis factor receptor superfamily [12–17]. TWEAK was initially recognized as a pro-apoptotic cytokine in tumor cells but it also facilitates promotion of inflammation and angiogenesis [12]. Of interest, TWEAK expression was markedly up-regulated in the injured brain tissues of mice after ischemic stroke [24]. Also, the TWEAK receptor Fn14 expression was significantly enhanced [24]. Of note, TWEAK exacerbated ischemic brain injury because a neutralizing anti-TWEAK antibody decreased the infarct size [32]. In addition, a soluble Fn14-Fc decoy receptor and genetic deficiency of Fn14 lessened the infarct size [33]. Such evidence indicates that TWEAK might exert a detrimental effect on neurological functions. TWEAK–Fn14 seems to promote ischemic brain damage through at least one mechanism, namely anti-inflammation, because recombinant TWEAK could trigger apoptosis in neurons in vitro by activating the transcription factor nuclear factor-kappa B, and TWEAK could stimulate nuclear factor-kappa B activity in the ischemic brain [34]; alternatively, TWEAK increased the accumulation of inflammatory cells in the choroid plexus, disrupted blood brain barrier integrity, and enhanced neuronal damage in mice with neuropsychiatric lupus [35]. Recently, high levels of serum soluble TWEAK were found to be highly associated with neuroinflammation during multiple sclerosis [36]. Although serum TWEAK levels has been revealed to be significantly elevated in patients with ischemic stroke [24], no further correlations were analyzed between serum TWEAK levels and other inflammatory mediators. This study not only showed a profoundly elevation of serum sTWEAK levels, but also demonstrated the close relationship between serum sTWEAK levels and serum C-reactive protein levels, implying that serum sTWEAK might act as an inflammatory biomarker in traumatized brain injury.

A more recent study showed that TWEAK serum levels were increased in multiple sclerosis patients, in relation to the disease activity [36]. In ischemic stroke, due to a small sample size (27 patients), a correlative analysis was not performed between serum TWEAK levels and disease severity [24]. In this study, GCS score was estimated to

reflect trauma severity. Our statistical analysis verified a strong and inverse correlation of serum sTWEAK levels with GCS score, which was whether regarded as a categorical variable or a continuous variable. Hence, it is presumed that serum sTWEAK could be considered as a biomarker for assessment of trauma severity after sTBI.

. We followed up sTBI patients until death or the completion of 6 months after head trauma. The mortality and functional outcome were recorded to evaluate the prognosis of sTBI patients. Moreover, GOS was identified as a continuous variable and also as a categorical variable. Meanwhile, GOS score of 1–3 was referred to as a poor outcome. All statistical results demonstrated that serum sTWEAK levels were in negative and intimate association with GOS scores, indicating that serum sTWEAK, to some extent, might serve as a prognostic biomarker for sTBI. Furthermore, in this study, patients dying within six months after head trauma or experiencing poor outcome at 6 months following trauma exhibited considerably high serum sTWEAK levels, in comparison with other remaining one. Notably, we continued to establish the three multivariate models for exploring the independent predictors for 6-month mortality, poor outcome and overall survival. Intriguingly, besides GCS score and presence of unreactive pupils, serum sTWEAK levels emerged as an independent predictor for the aforementioned prognostic parameters. Under ROC curve, serum sTWEAK levels possessed high ability for discriminating six-month mortality and for differentiating between patients with the development of 6-month poor outcome and those presenting with good outcome. Overall, it is presumed that serum sTWEAK could represent a potential biomarker for prognostication in head trauma.

5. Conclusions

The novel findings are that enhanced serum sTWEAK levels are significantly associated with decreasing GCS scores and GOS scores in addition to increasing serum C-reactive protein levels as well as that serum sTWEAK displays independent relation to 6-month mortality, overall survival and poor outcome, substantializing serum sTWEAK as a promising inflammatory biomarker for prognostic prediction and severity assessment.

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