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ORIGINAL RESEARCH

A Prospective Longitudinal Cohort Study of Serum Stanniocalcin-1 as a Potential Prognostic Biomarker of Severe Traumatic Brain Injury

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Background: Stanniocalcin-1 (STC1) may harbor anti-inflammatory and anti-oxidative properties, thereby exerting neuroprotective effects. This study was done with the intent to determine the role of serum STC1 in severity assessment and prognosis prediction of severe traumatic brain injury (sTBI).

Methods: In this prospective longitudinal cohort study of 104 sTBI patients and 104 healthy individuals (controls), serum STC1 levels were quantified. Severity indicators were Glasgow Coma Scale (GCS) and Rotterdam computed tomography classification. Follow-up time was 180 days and extended Glasgow outcome scale (GOSE) score 1–4 was deemed as poor prognosis. Multivariate analyses were applied to assess severity correlations and prognosis associations. Discriminative efficiencies were estimated in terms of area under receiver operating characteristic curve (AUC).

Results: Patients exhibited significantly higher serum STC1 levels than controls. Serum STC1 levels were substantially elevated in order of GCS scores from 8 to 3, Rotterdam scores from 3 to 6 and 180-day GOSE scores from 8 to 1. Also, serum STC1 levels were independently correlated with GCS scores, Rotterdam scores and 180-day GOSE scores. Serum STC1 levels were independently associated with 180-day death, overall survival and poor prognosis, as well as were efficiently predictive of death and poor prognosis. Prediction model containing GCS scores, Rotterdam scores and serum STC1 levels, as opposed to any of them, showed higher discriminative ability for the risks of death and poor prognosis. Alternatively, serum STC1 levels were linearly correlated with risk of death, overall survival and poor prognosis under restricted cubic spline. Subgroup analysis showed that serum STC1 levels non-statistically significantly interacted with age, gender, hypertension, diabetes mellitus, etc.

Conclusion: A significant elevation of serum STC1 levels is highly related to severity and clinical outcome, suggesting that serum STC1 may be a potential prognostic biomarker of sTBI.

Keywords: traumatic brain injury, stanniocalcin-1, severity, outcome, biomarkers

Introduction

Traumatic brain injury (TBI) is an external mechanical insult to the brain that damages neuronal cells and impairs neurologic function.[1] Road traffic accident is the primary cause of TBI, followed by falls.[2] One-third to half of trauma-related deaths are primarily caused by TBI, affecting 15–20/100,000 individuals annually.[2] Severe TBI (sTBI) accounts for 8% of all TBI worldwide, with approximately 5.48 million people suffering from sTBI annually.[3] sTBI mortality is from 20% to 30% and its prognosis is mainly related to trauma severity.[3] Secondary brain injury following sTBI involves hemorrhagic and ischemic cerebral injury, and the specific pathophysiological mechanisms include inflammatory reaction, mitochondrial dysfunction, cortical spreading depression, oxidative stress, microvascular thrombosis, neuronal necrosis and apoptosis, brain edema and blood–brain barrier disruption.[4] Conventionally, the Glasgow coma scale (GCS) is selected as a clinical severity indicator, which can be used to discriminate the risk of poor clinical outcome of sTBI.[5] The Rotterdam computed tomography (CT)

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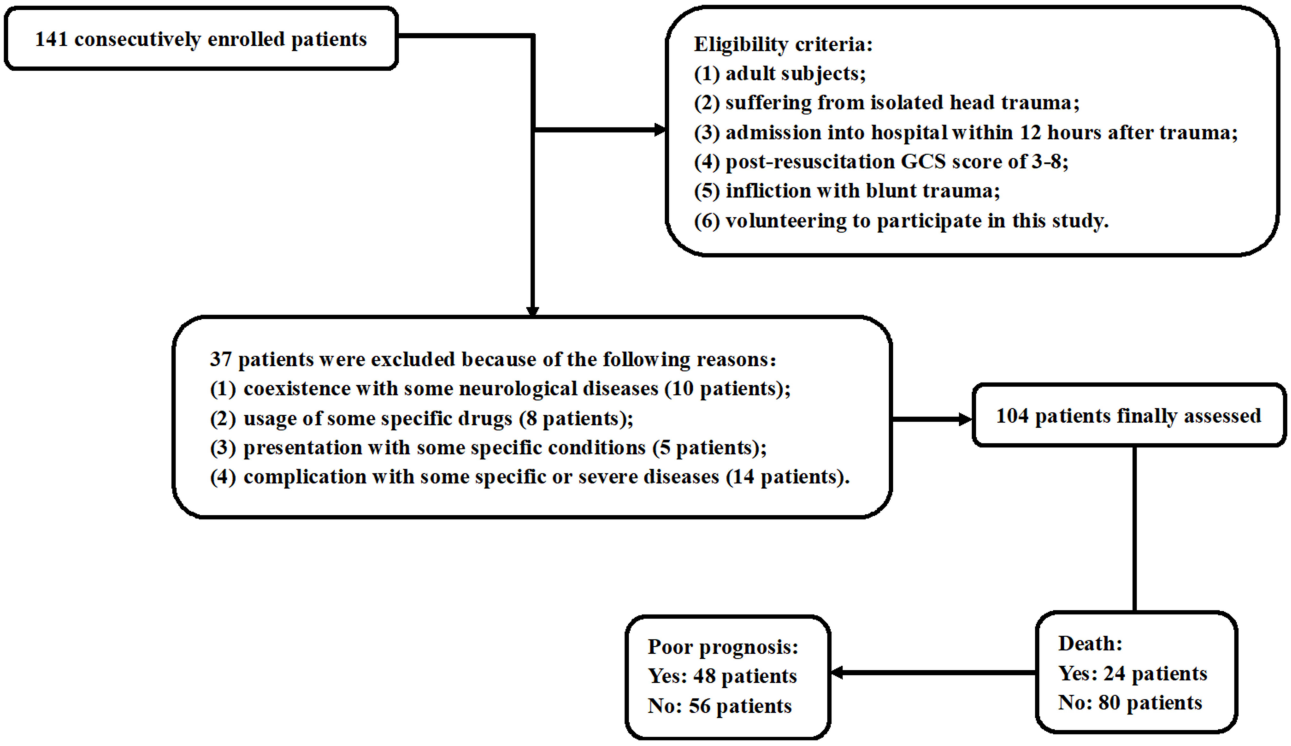

Figure 1 Flowing-chart showing selection of eligible patients. After screening 141 patients, 37 patients were removed from this study and finally 104 patients were further analyzed.
Abbreviation: GCS denotes Glasgow coma scale.

scale is accepted as a radiological tool, which has been frequently applied to evaluate head injury severity.[6] Generally, extended Glasgow Outcome Scale (GOSE), ranging from 1 to 8, is believably a valuable contribution to clinical outcome estimation at present.[7] During the past decades, researches have paid extensive attentions to exploration of prognostic biomarkers in head trauma.[8]

Stanniocalcin-1 (STC1) is described as a 56-kDa homodimeric glycoprotein hormone, that was initially found in bony fish.[9] Although STC1's precise functions warrant to be explored, it has been conceivably implicated in regulating calcium and phosphate homeostasis.[10] Gradually, compelling evidence has pointed to the notion that up-regulation of STC1 expressions under hypoxic conditions may display anti-inflammatory and anti-oxidative properties.[11–14] Clearly, STC1 is extensively expressed by neurons and glial cells in the normal brain.[15,16] Also,

Table 1 Baseline Characteristics of All Patients and Factors in Correlation with Serum Stanniocalcin-1 Levels After Severe Traumatic Brain Injury

	All Patients	ρ	*P* value
Gender (male/female)	58/46	−0.142	0.150
Age (years)	41.1±13.0	−0.053	0.596
Cigarette smoking	30 (28.9%)	0.096	0.332
Alcohol consumption	36 (34.6%)	0.008	0.938
Hypertension	18 (17.3%)	0.106	0.285
Diabetes mellitus	13 (12.5%)	0.158	0.108
Dyslipidemia	22 (21.2%)	0.102	0.305
Previous antihypertensive use	14 (13.5%)	0.042	0.670
Previous hypoglycemic or insulin use	10 (9.6%)	0.126	0.202
Previous statin use	16 (15.4%)	0.111	0.262

(*Continued*)

Table 1 (Continued).

	All Patients	ρ	P value
Admission time (h)	4.6 (3.6–6.1)	−0.096	0.332
Blood-collection time (h)	5.7 (4.5–7.6)	−0.131	0.186
Traumatic causes		0.030	0.759
Automobile/motorcycle	56		
Fall/jump	38		
Others	10		
GCS scores	5 (4–7)	−0.670	<0.001
Systolic AP (mmHg)	125.3 ± 22.0	−0.066	0.506
Diastolic AP (mmHg)	74.0± 12.5	−0.070	0.481
Mean AP (mmHg)	90.9± 15.2	−0.064	0.516
Rotterdam CT scores	4 (4–5)	0.689	<0.001
Abnormal cisterns	79 (76.0%)	0.230	0.019
Midline shift > 5 mm	63 (60.6%)	0.257	0.008
Epidural hematoma	54 (51.9%)	0.114	0.247
Subdural hematoma	60 (57.7%)	0.119	0.230
Subarachnoid hemorrhage	69 (66.3%)	0.224	0.022
Intraventricular hemorrhage	13 (12.5%)	0.066	0.503
Intracerebral hematoma	57 (54.8%)	0.060	0.548
Brain contusion	62 (59.6%)	0.183	0.063
Pneumocephalus	40 (38.5%)	0.021	0.829
Operation within 24 hours	42 (40.4%)	0.185	0.060
Seizure	27 (26.0%)	0.049	0.624
Blood glucose levels (mmol/l)	8.3 (6.1–11.9)	0.098	0.321
Blood WBC count ($\times 10^9$/l)	8.7 (6.9–10.2)	0.094	0.342

Note: Spearman test was used for bivariate correlation analysis.
Abbreviations: CT indicates computed tomography; GCS, Glasgow coma scale; AP, arterial pressure; WBC, white blood cell.

increased expressions of STC1 have been demonstrated in animal experiments like cerebral ischemia, TBI and sepsis-associated encephalopathy.[17–19] Moreover, in vitro study showed that overexpression of STC1 significantly enhanced neuronal resistance to hypoxia and hypercalcemia.[16] Similarly, STC1 obviously improved neurological

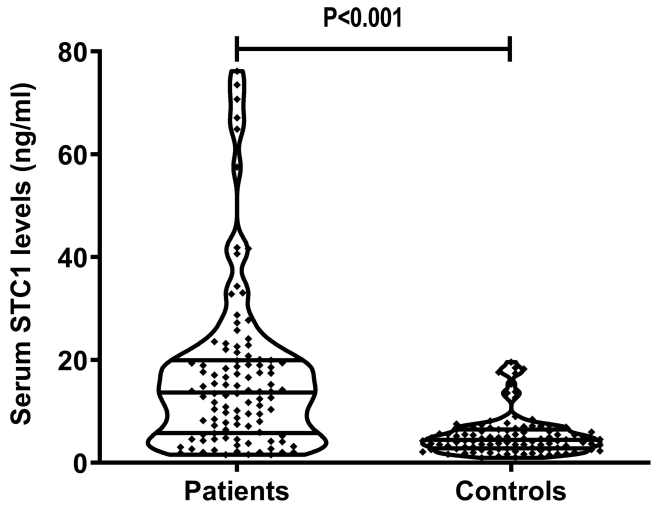

Figure 2 Scatter graph showing comparison of serum stanniocalcin-1 levels between controls and patients with severe traumatic brain injury. Serum stanniocalcin-1 levels were significantly lower in controls than in patients with severe traumatic brain injury (P<0.001).
Abbreviation: STC1 indicates stanniocalcin-1.

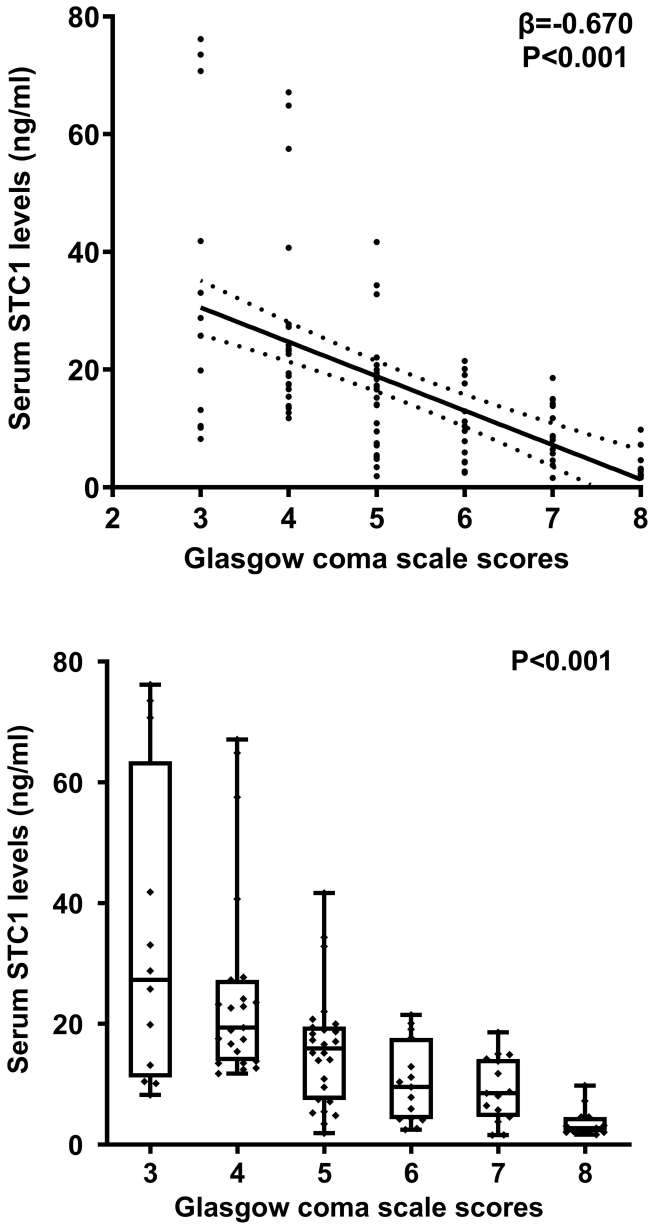

Figure 3 Scatter graph depicting relationship between serum stanniocalcin-1 levels and admission Glasgow coma scale scores after severe traumatic brain injury. Serum stanniocalcin-1 levels were significantly correlated with Glasgow coma scale scores (P<0.001) and were substantially decreased in the order of Glasgow coma scale scores from 3 to 8 (P<0.001).
Abbreviation: STC1 indicates stanniocalcin-1.

functions of animals with acute ischemic stroke or sepsis-associated encephalopathy and such effects may be achieved via its anti-oxidative and anti-inflammatory effects.[17,18] Hence, STC1 may act as a neuroprotective factor. Reportedly, a significant enhancement of serum STC1 levels was tightly related to the severity and poor clinical outcome of humans with aneurysmal subarachnoid hemorrhage.[20] Herein, we attempted to explore its value as a prognostic marker of sTBI.

Materials and Methods

Study Design, Subject Selection and Ethical Consent

The current study between April 2018 and October 2021 was divided into the two sub-studies: one was the case–control study and the other was the prospective observational cohort study. Cases in the case–control study were

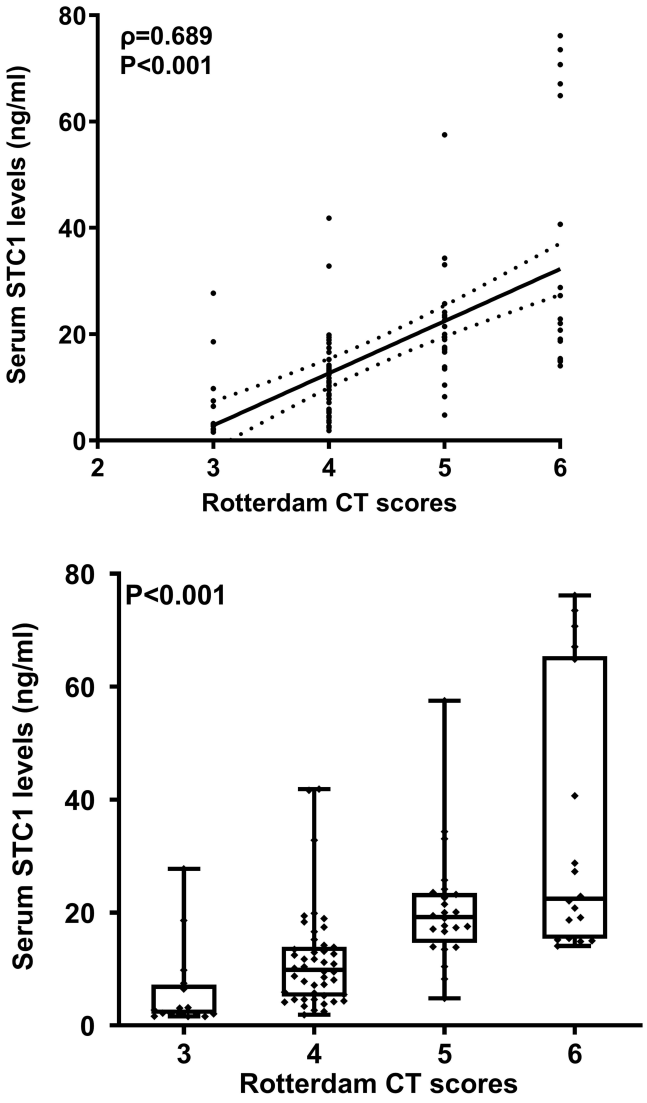

Figure 4 Scatter graph depicting relationship between serum stanniocalcin-1 levels and admission Rotterdam computed tomography scores after severe traumatic brain injury. Serum stanniocalcin-1 levels were significantly correlated with Rotterdam computed tomography scores (P<0.001) and were substantially increased in the order of Rotterdam computed tomography scores from 3 to 6 (P<0.001).
Abbreviations: STC1 indicates stanniocalcin-1; CT, computed tomography.

patients who were assessed in the prospective observational cohort study. The ethical guidelines of the Declaration of Helsinki and its later amends were strictly obeyed during the study. The study protocol was endorsed by the Institutional Review Committee at the Shaoxing People's Hospital (No. SH2018007). Participants volunteered to attend the current study, and the legal representatives of patients and controls themselves signed informed consent preceding the study.

The study cases were a group of patients with head trauma, who were consecutively recruited. The inclusion criteria were below: (1) patients were adults (namely, an age of 18 years or greater); (2) patients suffered from isolated head trauma (ie, injury severity score less than 9 in non-cranial aspects); (3) patients were admitted into hospital within 12 hours after trauma; (4) patients sustained sTBI (ie, post-resuscitation GCS score of 3–8); (5) patients were inflicted with blunt trauma; (6) patients were voluntary to participate in this study. The exclusion criteria were as follows: (1) sufferings from some neurological diseases, such as stroke, intracranial tumors, craniocerebral injury and Alzheimer's disease; (2) usages of some specific drugs, like hormones, anticoagulants and antiplatelet agents; (3) presentations with some specific conditions, for example pregnancies, missed visits,

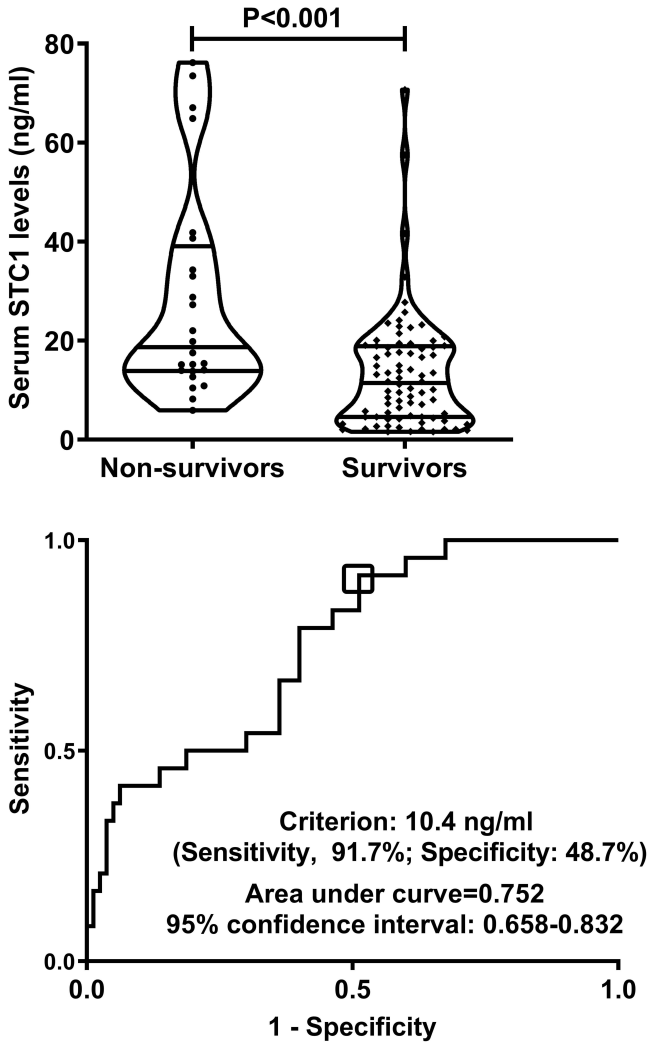

Figure 5 Relationship between serum stanniocalcin-1 levels and 180-day death following severe traumatic brain injury. Serum stanniocalcin-1 levels were markedly higher in non-survivors than in survivors (P<0.001) and had significantly discriminatory ability for the risk of death at 180 days after head trauma under receiver operating characteristic curve.
Abbreviation: STC1 indicates stanniocalcin-1.

unavailable samples and incomplete information; (4) complications with some specific or severe diseases, for instance recent infections, autoimmune diseases, malignancies and severe illnesses in heart, liver, lung and kidney.

Controls were selected from healthy volunteers. They were free from some chronic comorbidities, such as hypertension, diabetes mellitus and coronary heart disease. And some conventional tests, such as blood white blood cell counts, blood platelet counts, blood red blood cell counts and blood glucose levels, were in normal range.

Clinical Data and Outcome Assessment

Some conventional data, including age, gender, cigarette smoking, alcohol drinking, hypertension, diabetes mellitus, dyslipidemia, anticoagulative use, antiplatelet use, statin use, antihypertensive use, hypoglycemic use and insulin use. Traumatic causes referred to automobile/motorcycle, fall/jump, or others. Arterial blood pressure was non-invasively measured. We registered hospital admission time since trauma and recorded positive radiological characteristics, including intracranial hematoma, subarachnoid or intraventricular hemorrhage, brain contusion and pneumocephalus. In addition, abnormal cisterns were observed and midline shift was measured.

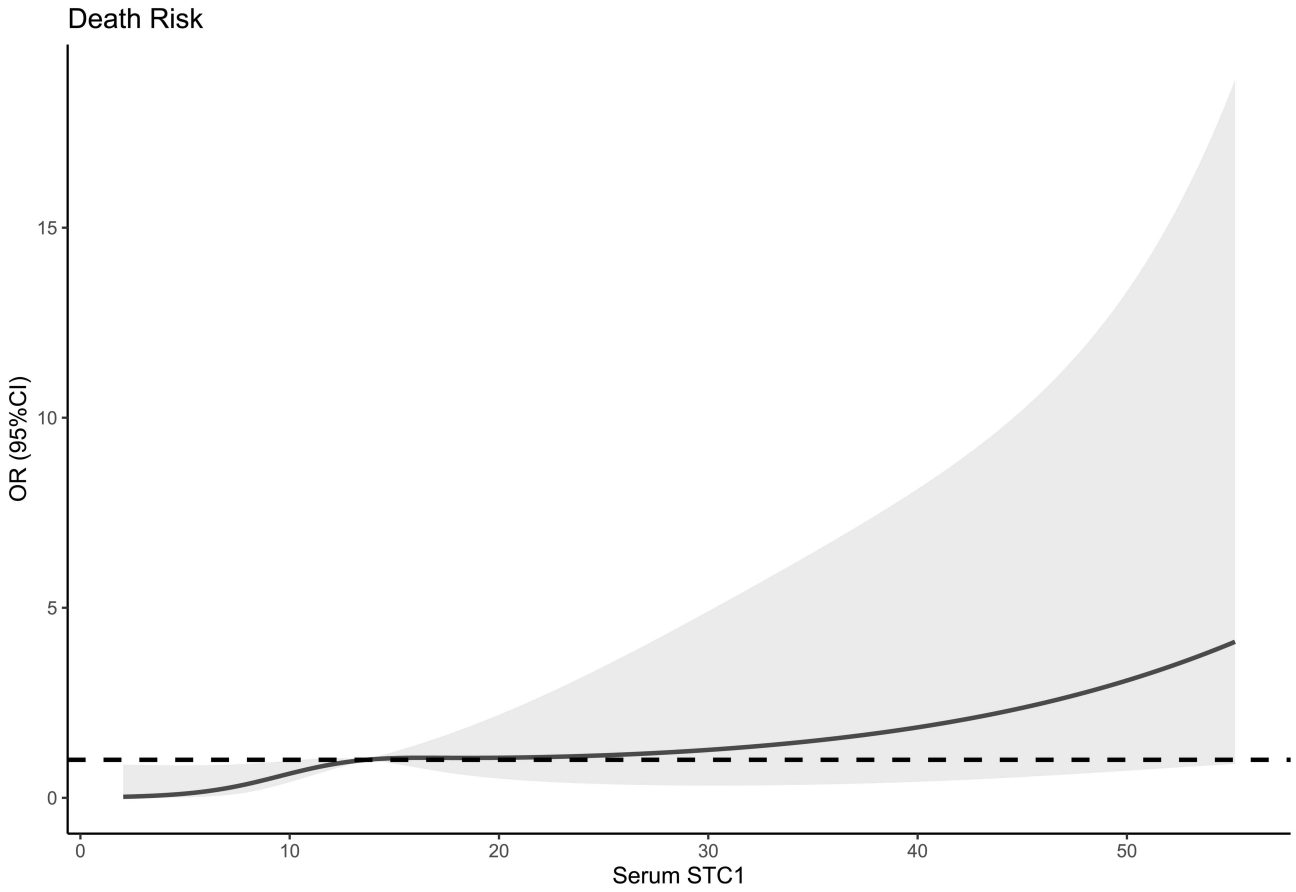

Figure 6 Restricted cubic spline demonstrating linear relation of serum stanniocalcin-1 levels with death risk. Serum stanniocalcin-1 levels were linearly correlated with death risk.
Abbreviations: STC1 indicates stanniocalcin-1; OR, odds ratio; 95% CI, 95% confidence interval.

Post-resuscitation GCS and Rotterdam CT scale were selected as the two severity indicators. We noticed whether patients underwent urgent operation within 24 hours after head trauma or suffered from seizure. GOSE was designated as a prognostic parameter and post-trauma 180-day GOSE score of 1–4 was deemed as a poor prognosis.[21]

Table 2 Factors in Association with 180-Day Death After Severe Traumatic Brain Injury

	Non-Survivors	Survivors	*P* value
Gender (male/female)	13/11	45/35	0.857
Age (years)	41.2±13.0	40.8±13.1	0.895
Cigarette smoking	10 (41.7%)	20 (25.0%)	0.114
Alcohol consumption	11 (45.8%)	25 (31.3%)	0.188
Hypertension	6 (25.0%)	12 (15.0%)	0.355
Diabetes mellitus	5 (20.8%)	8 (10.0%)	0.172
Dyslipidemia	6 (25.0%)	16 (20.0%)	0.599
Previous antihypertensive use	5 (20.8%)	9 (11.3%)	0.304
Previous hypoglycemic or insulin use	3 (12.5%)	7 (8.8%)	0.693
Previous statin use	4 (16.7%)	12 (15.0%)	1.000
Admission time (h)	4.5 (3.4–5.6)	4.7 (3.6–6.3)	0.578
Blood-collection time (h)	5.3 (4.2–7.1)	6.0 (4.5–7.7)	0.459

(*Continued*)

Table 2 (Continued).

	Non-Survivors	Survivors	*P* value
Traumatic causes			0.125
Automobile/motorcycle	15	41	
Fall/jump	5	33	
Others	4	6	
GCS scores	4 (3–5)	6 (5–7)	<0.001
Systolic AP (mmHg)	123.8±24.6	125.7±21.4	0.712
Diastolic AP (mmHg)	74.0±14.0	73.9±12.2	0.968
Mean AP (mmHg)	89.8±16.4	91.3±14.9	0.680
Rotterdam CT scores	5 (4–6)	4 (4–5)	<0.001
Abnormal cisterns	23 (95.8%)	56 (70.0%)	0.009
Midline shift > 5 mm	20 (83.3%)	43 (53.8%)	0.009
Epidural hematoma	16 (66.7%)	38 (47.5%)	0.099
Subdural hematoma	15 (62.5%)	45 (56.3%)	0.587
Subarachnoid hemorrhage	20 (83.3%)	49 (61.3%)	0.045
Intraventricular hemorrhage	4 (16.7%)	9 (11.3%)	0.491
Intracerebral hematoma	16 (66.7%)	41 (51.3%)	0.183
Brain contusion	15 (62.5%)	47 (58.8%)	0.743
Pneumocephalus	11 (45.8%)	29 (36.3%)	0.397
Operation within 24 hours	13 (54.2%)	29 (36.3%)	0.117
Seizure	8 (33.3%)	19 (23.8%)	0.348
Blood glucose levels (mmol/l)	9.4 (7.4–11.3)	7.8 (5.7–12.4)	0.064
Blood WBC count ($\times 10^9$/l)	7.5 (6.3–10.4)	8.8 (7.1–10.2)	0.371
Serum stanniocalcin-1 levels (ng/mL)	18.7 (13.9–37.5)	11.5 (4.6–18.8)	<0.001

Notes: Variables were presented as count (proportion), median (lower-upper quartiles) or mean ± standard deviation where appropriate. Statistical analysis was conducted using the Pearson's Chi-square test, Mann–Whitney *U*-test or independent *t* test as appropriate.
Abbreviations: CT indicates computed tomography; GCS, Glasgow coma scale; AP, arterial pressure; WBC, white blood cell.

Immune Analysis

The blood of the median cubital vein was drawn from the admitted patients, and time of blood-collection since trauma was recorded. Also, we acquired their blood samples when controls were selected into this study. Blood samples were very soon put in 5 mL gel-containing biochemistry tubes, and after centrifugation, an aliquot of serum sample was extracted and afterwards preserved at a −80°C freezer for further immune analysis. Serum STC1 levels were quantified in batches. Because the biomarkers may be unstable, serum STC1 levels were in batches measured. Blood samples, which were thawed every three months, were used for measuring serum STC1 levels. The sandwich enzyme linked immunosorbent assay kit was purchased from Wuhan Fine Biotech Co., Ltd. (Wuhan, China). Detection range of the reagent kit was from 78.125 to 5000 pg/mL, with sensitivity of 46.875 pg/mL. Its intra-assay coefficient of variation was <8%, with inter-assay coefficient of variation of <10%. Using blind method, all quantifications were in duplicate actualized by the same experienced technician. Double measurements were averaged for statistical analysis.

Statistical Analysis

In the current study, the receiver-operating characteristic (ROC) curve was configured and areas under ROC curve (AUCs) were compared using MedCalc statistical software version 17.4 (MedCalc Software, Mariakerke, Belgium). Other statistical analyses, including bivariate correlations, multivariate analyses and intergroup comparisons, were done using the SPSS statistical package version 20.0 (SPSS Inc., Chicago, Illinois, USA). All graphs were plotted using GraphPad Prism statistical software version 8 (GraphPad Software, San Diego, CA, USA). Data were presented as counts (percentages) if they were categorical variables, means (standard

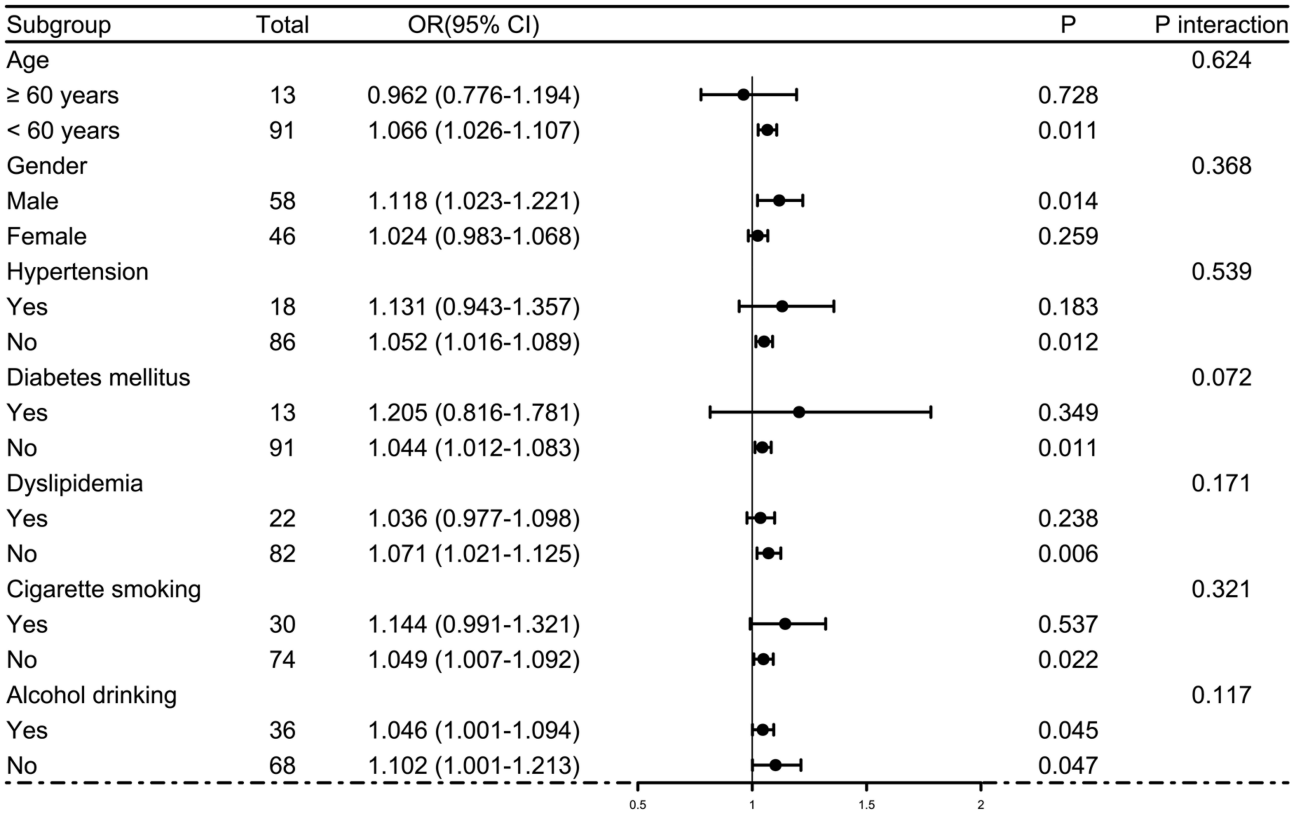

Figure 7 Subgroup analysis verifying interaction between serum stanniocalcin-1 levels and other variables for predicting death. No interactions were found between serum stanniocalcin-1 levels and other variables, such as age, gender and hypertension (all P interaction >0.05).
Abbreviations: OR means odds ratio; 95% CI, 95% confidence interval.

deviations, SDs) if they were normally distributed continuous variables and medians (upper-lower quartiles) if they were non-normally distributed continuous variables. Statistical methods for comparing data between two groups included the Pearson's Chi-square test, independent *t*-test and Mann–Whitney *U*-test. Using the Kruskal–Wallis *H*-test, data were compared among multiple groups. Using the Spearman test, bivariate correlations were analyzed. The two multivariate linear regression models, where serum STC1 levels and 180-day GOSE scores were considered as the dependent variables, were constructed to discover independent correlative factors. The two binary logistic regression models, where 180-day death and poor prognosis were selected as the dependent variables, were built to discern independent predictors. The Log rank test was performed to complete the comparison of 180-day overall survival time between two groups. The multivariate Cox's proportional hazard model, where 180-day overall survival time was regarded as the dependent variable, were established to ascertain independent predictive parameters. The combined logistic regression model, integrating serum STC1 levels, GCS scores and Rotterdam CT scores, was formed to explore the additive effect of serum STC1 levels on GCS scores and Rotterdam CT scores. Z test was enforced for comparisons of AUCs. Restricted cubic spline was in use for demonstrating whether serum STC1 levels were linearly related to 180-day mortality, overall survival and poor prognosis. Subgroup analysis was utilized to investigate interaction between serum STC1 levels and other variables, such as age, gender and chronic diseases. The sample size calculation was completed using the MedCalc statistical software version 17.4 (MedCalc Software, Mariakerke, Belgium). In sample size module, whether in bivariate correlation analyses, intergroup comparisons, ROC curve analyses or others, a group of 104 patients were deemed adequate for clinical investigation. The two-sided P-values <0.05 were deemed as statistically significant differences.

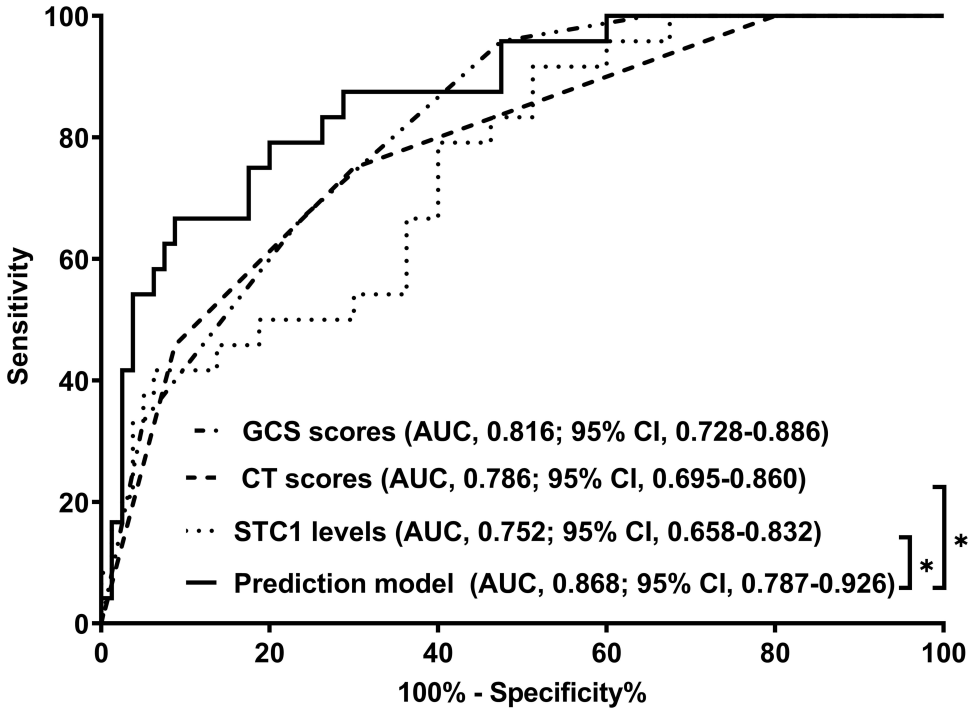

Figure 8 Receiver operating characteristic curves showing comparisons of various variables for prediction of death at 180 days after severe traumatic brain injury. Serum stanniocalcin-1 levels displayed similar death predictive ability, as compared to Glasgow coma scale scores and Rotterdam computed tomography scale scores (both P>0.05). Prediction model integrating serum stanniocalcin-1 levels, Glasgow coma scale scores and Rotterdam computed tomography scale scores, showed significantly higher death predictive capability than serum stanniocalcin-1 levels and Rotterdam computed tomography scale scores (both P<0.05), but not Glasgow coma scale scores. *P<0.05.
Abbreviations: STC1 indicates stanniocalcin-1; GCS, Glasgow coma scale; CT, computed tomography; AUC, area under curve; 95% CI, 95% confidence interval.

Results

Participant Characteristics

During this study, an initial assessment was done of 141 adults with isolated blunt sTBI, who were chosen according to the prespecified inclusion criteria. Based on the presented exclusion criteria, 37 patients were removed from the present study because of the reasons outlined in Figure 1. Finally, a total of 104 patients were deemed as eligibility for further clinical investigation. The baseline characteristics of patients are listed in Table 1. Simultaneously, an aggregate of 104

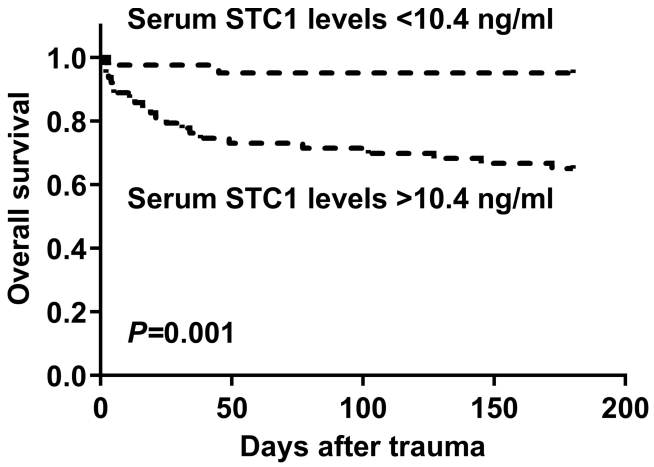

Figure 9 Survival curve showing 180-day death after severe traumatic brain injury across serum stanniocalcin-1 levels. 180-day overall survival time was significantly lower in patients with serum stanniocalcin-1 levels above 10.4 ng/mL than in those with serum stanniocalcin-1 levels below 10.4 ng/mL (P<0.01).
Abbreviation: STC1 indicates stanniocalcin-1.

Table 3 Factors in Correlation with 180-Day Overall Survival After Severe Traumatic Brain Injury

	HR	95% CI	*P* value
Gender (male/female)	0.935	0.419–2.087	0.870
Age (years)	0.997	0.967–1.029	0.873
Cigarette smoking	1.778	0.790–4.003	0.165
Alcohol consumption	1.638	0.734–3.656	0.229
Hypertension	1.643	0.652–4.141	0.292
Diabetes mellitus	2.099	0.784–5.624	0.140
Dyslipidemia	1.268	0.503–3.195	0.614
Previous antihypertensive use	1.689	0.630–4.525	0.298
Previous hypoglycemic or insulin use	1.339	0.399–4.490	0.636
Previous statin use	1.085	0.371–3.175	0.881
Admission time (h)	0.970	0.821–1.146	0.719
Blood-collection time (h)	0.944	0.803–1.110	0.485
Traumatic causes			
Automobile/motorcycle	1		
Fall/jump	0.566	0.188–1.708	0.313
Others	0.269	0.072–1.003	0.051
GCS scores	0.415	0.281–0.611	<0.001
Systolic AP (mmHg)	0.998	0.979–1.016	0.798
Diastolic AP (mmHg)	1.003	0.970–1.037	0.866
Mean AP (mmHg)	0.996	0.970–1.023	0.777
Rotterdam CT scores	2.721	1.718–4.310	<0.001
Abnormal cisterns	8.208	1.108–60.801	0.039
Midline shift > 5 mm	3.688	1.260–10.796	0.017
Epidural hematoma	2.052	0.878–4.795	0.097
Subdural hematoma	1.304	0.570–2.979	0.530
Subarachnoid hemorrhage	2.894	0.989–8.470	0.052
Intraventricular hemorrhage	1.443	0.493–4.224	0.503
Intracerebral hematoma	1.726	0.739–4.033	0.208
Brain contusion	1.142	0.500–2.611	0.752
Pneumocephalus	1.472	0.660–3.287	0.345
Operation within 24 hours	1.867	0.836–4.168	0.128
Seizure	1.521	0.651–3.554	0.333
Blood glucose levels (mmol/l)	1.053	0.965–1.149	0.248
Blood WBC count ($\times 10^9$/l)	0.937	0.785–1.117	0.466
Serum stanniocalcin-1 levels (ng/mL)	1.043	1.025–1.061	<0.001

Notes: Univariate Cox's proportional hazard regression analysis was performed.
Abbreviations: CT indicates computed tomography; GCS, Glasgow coma scale; AP, arterial pressure; WBC, white blood cell; HR, hazard ratio; 95% CI, 95% confidence interval.

controls were recruited. Controls were aged from 18 to 75 years (mean, 42.2 years; SD, 13.8 years), among whom there were 57 males, 29 cigarette smokers and 33 alcohol drinkers. No statistically significant differences were shown across age, gender, alcohol consumption and cigarette smoking between patients and controls (all P>0.05).

Serum STC1 Levels Following STBI and Its Relation to Severity

As opposed to controls, serum STC1 levels were substantially enhanced in patients with sTBI (P<0.001; Figure 2). For the sake of correlative analysis between serum STC1 levels and trauma severity, GCS scores and Rotterdam CT scores were selected as the severity parameters and were considered as the categorical or continuous variables. In Figure 3,

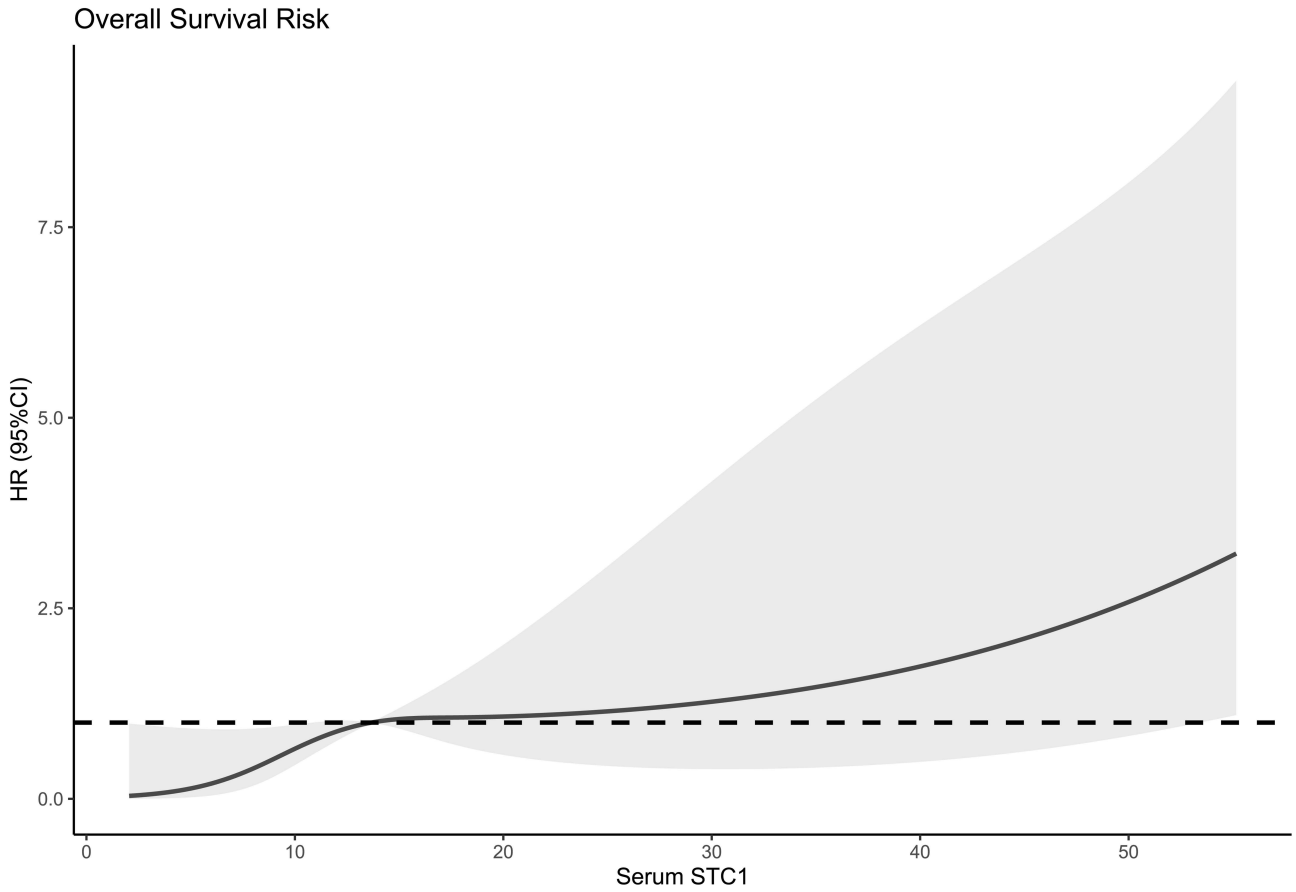

Figure 10 Restricted cubic spline demonstrating linear relation of serum stanniocalcin-1 levels with overall survival risk. Serum stanniocalcin-1 levels were linearly correlated with overall survival risk.
Abbreviations: STC1 indicates stanniocalcin-1; HR, hazard ratio; 95% CI, 95% confidence interval.

serum STC1 levels were inversely, significantly correlated with GCS scores (P<0.001) and were significantly decreased in the order of GCS scores from 3 to 8 (P<0.001). In Figure 4, there was a positive, substantial correlation between serum STC1 levels and Rotterdam CT scores (P<0.001); and serum STC1 levels were markedly lowest in patients with score 3, followed by scores 4 and 5, and were significantly highest in those with score 6 (P < 0.001). Besides GCS scores and Rotterdam CT scores, other variables, which were highly correlated with serum STC1 levels using Spearman test, were abnormal cisterns, midline shift > 5 mm and subarachnoid hemorrhage (all P<0.05; Table 1). Moreover, using the multivariate linear regression model, in which the preceding five significantly correlative variables were enforced, serum STC1 levels were independently related to GCS score (beta, −3.510; 95% CI; −5.391–1.629; VIF, 1.543; t=−3.703; P=0.007) and Rotterdam CT score (beta, 6.293; 95% CI; 3.288–9.299; VIF, 1.472; t=4.156; P=0.001).

Relationship Between Serum STC1 Levels and 180-Day Death Following sTBI

Post-trauma 180-day mortality was 23.1% (24/104) in this group of patients with sTBI. In Figure 5, serum STC1 levels were statistically significantly higher in non-survivors than in survivors (P<0.001). Moreover, serum STC1 levels had significantly discriminatory efficiency for the risk of 180-day death (P<0.001; Figure 5), and its optimal criterion was generated using the Youden method, which predicted 180-day death with the corresponding sensitivity and specificity values (Figure 5). As shown in Figure 6, serum STC1 levels were linearly related to risk of death under restricted cubic spline (P=0.125). In Table 2, non-survivors had significantly lower GCS scores than survivors (P<0.001), Rotterdam CT scores and serum STC1 levels were substantially higher in the death than in the alive (both P<0.001), and the dying patients displayed markedly higher percentages of subarachnoid hemorrhage, midline shift above 5 mm and abnormal cisterns than other remainders (all P<0.05).

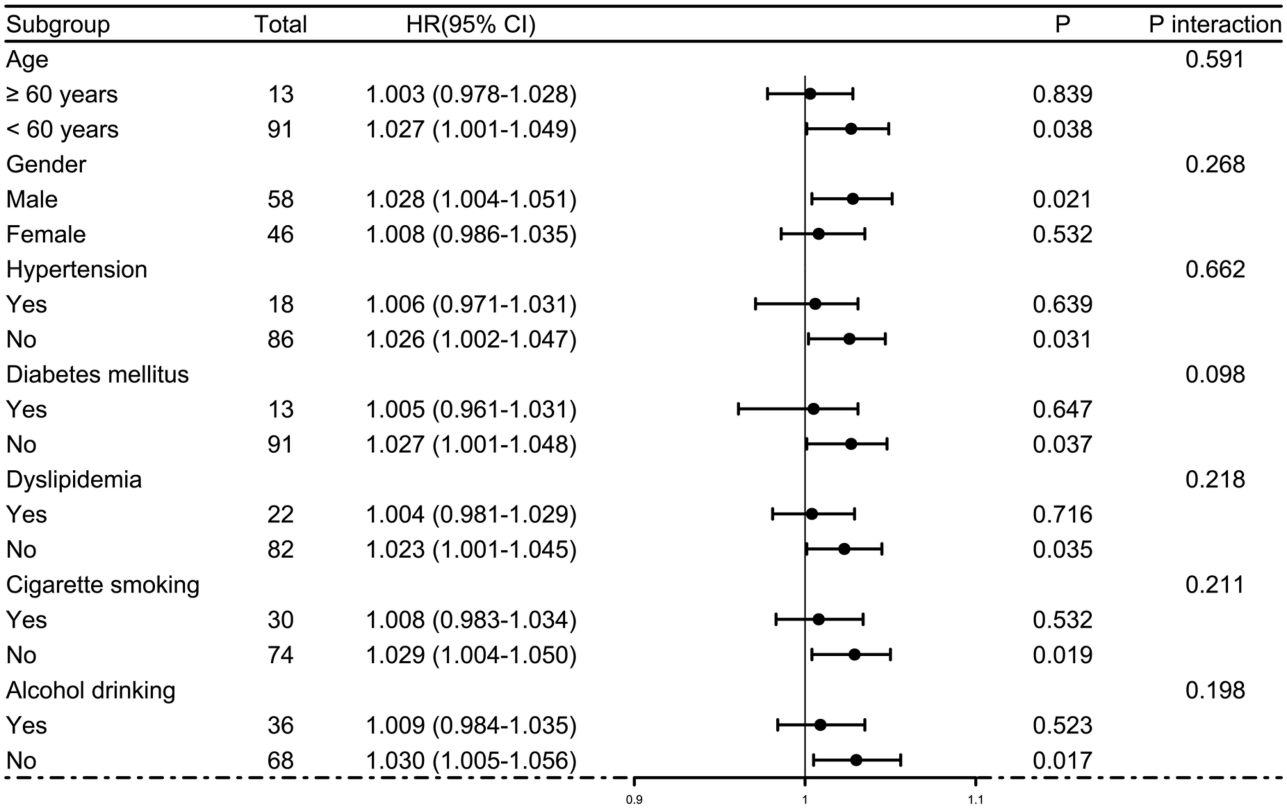

Figure 11 Subgroup analysis verifying interaction between serum stanniocalcin-1 levels and other variables for predicting overall survival. No interactions were found between serum stanniocalcin-1 levels and other variables, such as age, gender and hypertension (all P interaction >0.05).
Abbreviations: HR means hazard ratio; 95% CI, 95% confidence interval.

Using the binary logistic regression analysis, serum STC1 levels (OR, 1.059; 95% CI, 1.022–1.097; P=0.013), GCS scores (OR, 0.410; 95% CI, 0.213–0.789; P=0.002) and Rotterdam CT scores (OR, 2.823; 95% CI, 1.242–6.417; P=0.008) retained as the three independent predictors of 180-day death after trauma. Subgroup analysis confirmed that serum STC1 levels did not interact with age, gender, hypertension and so on (all P>0.05; Figure 7). Hosmer–Lemeshow test showed that prediction model, which integrated serum STC1 levels, GCS scores and Rotterdam CT scores, were comparatively stable (P=0.641). In Figure 8, AUC of serum STC1 levels was equivalent to those of GCS scores and Rotterdam CT scores (both P>0.05). Alternatively, AUC of prediction model was significantly higher than those of serum STC1 levels and Rotterdam CT scores (both P<0.05), but not that of GCS scores (P>0.05). Using the cutoff value of serum STC1 levels (10.4 ng/mL), which was identified under ROC curve (Figure 5), patients were dichotomized. As outlined in Figure 9, patients with serum STC1 levels >10.4 ng/mL had substantially shorter 180-day overall survival time than other remainders (P<0.01). GCS scores, Rotterdam CT scores, abnormal cisterns, midline shift >5 mm and serum STC1 levels were statistically significantly associated with 180-day overall survival (all P<0.05; Table 3). In the multivariate Cox's proportional hazard model, GCS scores (HR, 0.497; 95% CI, 0.321–0.769; P=0.002), Rotterdam CT scores (HR, 1.948; 95% CI, 1.079–3.515; P=0.005) and serum STC1 levels (HR, 1.024; 95% CI, 1.002–1.046; P=0.030) remained to be independently related to 180-day overall survival. In Figure 10, serum STC1 levels were linearly related to overall survival risk under restricted cubic spline (P=0.219). In Figure 11, using subgroup analysis, serum STC1 levels had no interaction with age, gender, hypertension and so on (all P>0.05).

Relation of Serum STC1 Levels to 180-Day Poor Outcome Following sTBI

In Figure 12, serum STC1 levels of patients were intimately correlated with GOSE scores at 180 days after head trauma (P<0.001) and were dramatically decreased in the order of GOSE scores from 1 to 8 (P<0.001). Using the Spearman test, there was a close correlation between GOSE scores and serum STC1 levels, between GOSE scores and GCS scores, between GOSE scores and Rotterdam CT scores, between GOSE scores and subarachnoid hemorrhage, between GOSE scores and abnormal cisterns, as well as between GOSE scores and midline shift above 5 mm (all P<0.05; Table 4). The multivariate analysis confirmed that GOSE scores were independently correlated with GCS scores (beta, 0.575; 95% CI; 0.309–0.841; VIF, 1.671; t=4.285; P=0.005), Rotterdam CT scores (beta, −0.995; 95% CI; −1.436–0.553; VIF, 1.717; t=−4.470; P=0.001) and serum STC1 levels (beta, −0.032; 95% CI; −0.059–0.005; VIF, 1.495; t=−2.372; P=0.020). Totally, forty-eight patients experienced a poor prognosis (GOSE scores of 1–4). Patients with a poor prognosis, in contrast to those presenting with a good prognosis, had significantly elevated serum STC1 levels (P<0.001; Figure 13). Serum STC1 levels were highly discriminative of a poor prognosis and its suitable cutoff value was 9.8 ng/mL using the maximum Youden index (Figure 13). In Table 5, as compared to patients with the development of a poor prognosis, those with a good prognosis displayed significantly increased GCS scores, exhibited substantially reduced Rotterdam CT scores, blood glucose levels and serum STC1 scores, as well as showed markedly declined proportions of subarachnoid hemorrhage, midline shift more than 5 mm and abnormal cisterns (all P<0.05). Using multivariable analysis, GCS scores, Rotterdam CT scores and serum STC1 levels predicted a poor prognosis with OR values of 0.383

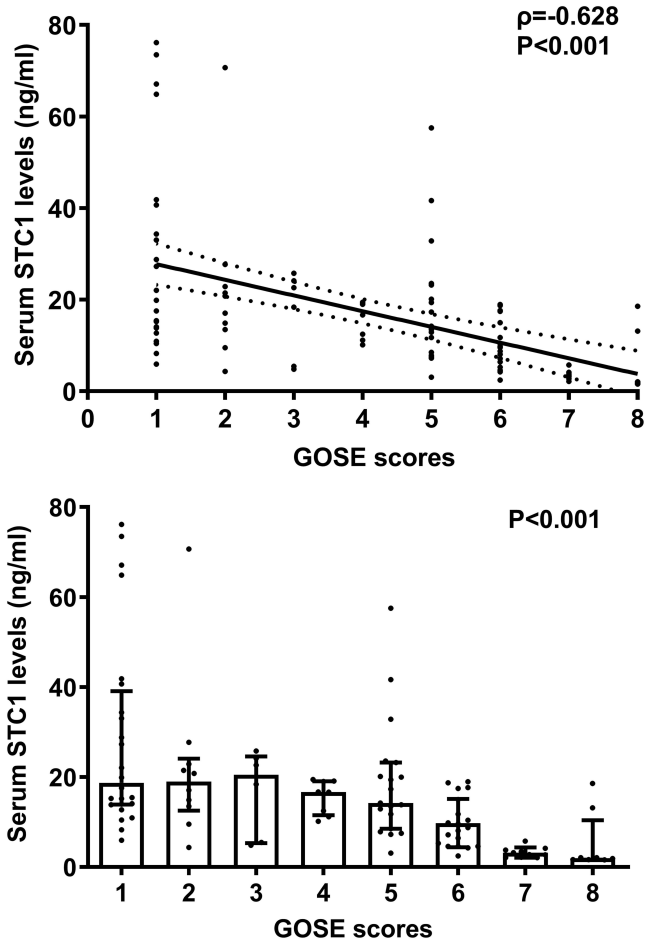

Figure 12 Scatter graph depicting relationship between serum stanniocalcin-1 levels and 180-day extended Glasgow outcome scale scores after severe traumatic brain injury. Serum stanniocalcin-1 levels were significantly correlated with 180-day extended Glasgow outcome scale scores (P<0.001) and were substantially reduced in the order of 180-day extended Glasgow outcome scale scores from 1 to 8 (P<0.001).
Abbreviations: STC1 indicates stanniocalcin-1; GOSE, extended Glasgow outcome scale.

Table 4 Factors in Correlation with Extended Glasgow Outcome Scale Scores at 180 Days After Severe Traumatic Brain Injury

	ρ	***P* value**
Gender (male/female)	0.090	0.362
Age (years)	−0.052	0.597
Cigarette smoking	−0.191	0.052
Alcohol consumption	−0.045	0.647
Hypertension	−0.048	0.628
Diabetes mellitus	−0.159	0.108
Dyslipidemia	−0.066	0.503
Previous antihypertensive use	−0.049	0.621
Previous hypoglycemic or insulin use	−0.081	0.414
Previous statin use	−0.036	0.720
Admission time (h)	0.102	0.305
Blood-collection time (h)	0.128	0.197
Traumatic causes	0.018	0.857
GCS scores	0.641	<0.001
Systolic AP (mmHg)	0.156	0.115
Diastolic AP (mmHg)	0.082	0.406
Mean AP (mmHg)	0.124	0.210
Rotterdam CT scores	−0.650	<0.001
Abnormal cisterns	−0.306	0.002
Midline shift > 5 mm	−0.329	0.001
Epidural hematoma	−0.123	0.213
Subdural hematoma	−0.109	0.270
Subarachnoid hemorrhage	−0.331	0.001
Intraventricular hemorrhage	−0.025	0.805
Intracerebral hematoma	−0.117	0.235
Brain contusion	−0.161	0.101
Pneumocephalus	−0.058	0.560
Operation within 24 hours	−0.126	0.202
Seizure	−0.083	0.405
Blood glucose levels (mmol/l)	−0.163	0.098
Blood WBC count ($\times 10^9$/l)	−0.120	0.223
Serum stanniocalcin-1 levels (ng/mL)	−0.628	<0.001

Note: Spearman test was used for bivariate correlation analysis.
Abbreviations: CT indicates computed tomography; GCS, Glasgow coma scale; AP, arterial pressure; WBC, white blood cell.

(95% CI, 0.228–0.646; P=0.001), 3.699 (95% CI, 1.719–7.958; P=0.008) and 1.071 (95% CI, 1.026–1.119; P=0.011). As depicted in Figure 14, serum STC1 levels had linear relation to risk of poor prognosis using restricted cubic spline (P=0.109). No interactions existed between serum STC1 levels and other variables, such as age, gender and hypertension (all P>0.05; Figure 15). Using Hosmer-Lemeshow test, prediction model combining them were relatively stable (P=0.272). In terms of AUC, prognostic predictive ability of serum STC1 levels resembled those of GCS scores and Rotterdam CT scores (all P>0.05); and that of prediction model was superior to any one of them (all P<0.05; Figure 16).

Discussion

To the best of our knowledge, until now it was unclear whether serum STC1 levels may be correlated with trauma severity and clinical outcomes after sTBI. Our study found that (1) there was a significant elevation of serum STC1 levels after sTBI in humans, as compared to healthy controls; (2) serum STC1 levels were

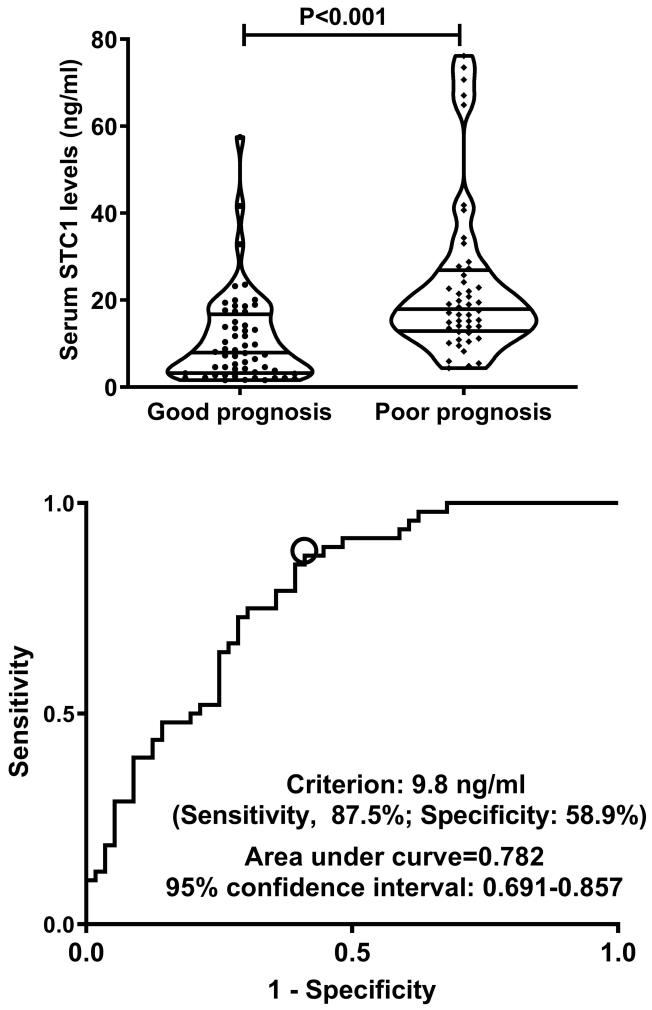

Figure 13 Relationship between serum stanniocalcin-1 levels and 180-day poor prognosis following severe traumatic brain injury. Serum stanniocalcin-1 levels were markedly higher in patients with poor prognosis than in those with poor prognosis (P<0.001) and exhibited substantially discriminatory ability for the risk of poor prognosis at 180 days after head trauma under receiver operating characteristic curve.
Abbreviation: STC1 indicates stanniocalcin-1.

intimately correlated with baseline GCS scores and Rotterdam CT scores after sTBI; (3) serum STC1 levels were closely associated with 180-day death, GOSE scores and poor prognosis following sTBI; (4) prediction model containing serum STC1 levels, GCS scores and Rotterdam CT scores efficiently discriminated the risk of death and poor prognosis at 180 days after sTBI. Taken together, the preceding data are supportive of the presumption that serum STC1 may be of significance as a potential biomarker in human sTBI.

Compelling data have demonstrated that STC1 may confer neuroprotective functions. STC1 could obviously reduce ischemic brain injury of rats suffering from global cerebral ischemia/perfusion and its effects may be dependent on anti-oxidative properties.[22] Using in vitro experimental data, it was revealed that STC1 could substantially protect cerebral neurons or astrocytes from hypoxic and ischemic damage and these effects may be related to regulating glycolysis and redox homeostasis.[16,23] Similarly, in a study containing in vitro and in vivo experiments, STC1 could significantly repress inflammatory response of microglia, thereby protecting rats against sepsis-associated encephalopathy.[17] Another experiment showed that STC1 may be relevant to hypoxic preconditioning-induced tolerance to brain ischemia in mice, with interleukin-6 –mediated expression of STC-1 as one molecular mechanism.[15] Also, in a study of rat ischemic stroke, STC1 may facilitate angiogenesis and thereby inhibit neuronal apoptosis.[24] Overall, it is clear that STCI may harbor brain-protective effects, while its influence mechanisms warrant to be further explored.

Table 5 Factors in Relation to 180-Day Poor Prognosis After Severe Traumatic Brain Injury

	Poor Prognosis	Good Prognosis	*P* value
Gender (male/female)	24/24	34/22	0.273
Age (years)	41.7 ± 12.8	40.5 ± 13.2	0.629
Cigarette smoking	17 (35.4%)	13 (23.2%)	0.171
Alcohol consumption	17 (35.4%)	19 (33.9%)	0.874
Hypertension	8 (16.7%)	10 (17.9%)	0.873
Diabetes mellitus	8 (16.7%)	5 (8.9%)	0.234
Dyslipidemia	10 (20.8%)	12 (21.4%)	0.941
Previous antihypertensive use	7 (14.6%)	7 (12.5%)	0.756
Previous hypoglycemic or insulin use	5 (10.4%)	5 (8.9%)	0.797
Previous statin use	7 (14.6%)	9 (16.1%)	0.834
Admission time (h)	4.6 (3.4–5.8)	4.7 (3.8–6.4)	0.292
Blood-collection time (h)	5.5 (4.3–7.3)	5.9 (4.7–7.8)	0.238
Traumatic causes			0.051
Automobile/motorcycle	26	30	
Fall/jump	14	24	
Others	8	2	
GCS scores	4 (4–5)	6 (5–7)	<0.001
Systolic AP (mmHg)	122.1 ± 23.2	128.0 ± 20.9	0.178
Diastolic AP (mmHg)	73.4 ± 14.4	74.4 ± 10.9	0.701
Mean AP (mmHg)	89.3 ± 16.6	92.4 ± 13.9	0.297
Rotterdam CT scores	5 (4–6)	4 (3–4)	<0.001
Abnormal cisterns	43 (89.6%)	36 (64.3%)	0.003
Midline shift > 5 mm	37 (77.1%)	26 (46.4%)	0.001
Epidural hematoma	29 (60.4%)	25 (44.6%)	0.108
Subdural hematoma	31 (64.6%)	29 (51.8%)	0.188
Subarachnoid hemorrhage	37 (77.1%)	32 (51.7%)	0.032
Intraventricular hemorrhage	7 (14.6%)	6 (10.7%)	0.552
Intracerebral hematoma	29 (60.4%)	28 (50.0%)	0.287
Brain contusion	32 (66.7%)	30 (53.6%)	0.175
Pneumocephalus	18 (37.5%)	22 (39.3%)	0.852
Operation within 24 hours	20 (41.7%)	22 (39.3%)	0.805
Seizure	15 (31.3%)	12 (21.4%)	0.255
Blood glucose levels (mmol/l)	9.5 (7.1–12.5)	7.7 (5.5–9.9)	0.020
Blood WBC count ($\times 10^9$/l)	9.1 (6.9–11.3)	8.2 (6.5–9.9)	0.224
Serum stanniocalcin-1 levels (ng/mL)	17.9 (13.1–26.5)	7.9 (3.3–16.2)	<0.001

Notes: Variables were presented as count (proportion), median (lower-upper quartiles) or mean ± standard deviation where appropriate. Statistical analysis was conducted using the Pearson's Chi-square test, Mann–Whitney *U*-test or independent *t*-test as appropriate.

Abbreviations: CT indicates computed tomography; GCS, Glasgow coma scale; AP, arterial pressure; WBC, white blood cell.

In central nervous system, STC1 is mainly expressed in neurons and glial cells.[16,23] Increased expressions of STC1 were found in astrocyte cell lines and astrocytes in the brain tissues of mice when exposed to hypoxia.[23] In a hypercalcemic culture medium, STC1 was prominently elicited from the human neural-crest-derived cell-line Paju.[16] Also, a histological study of human and rat brains showed that there was a remarkable upregulation of STC1 expressions in neurons surrounding the core of acute infarcts.[16] In addition, hypoxia could obviously promote STC1 expressions in the brain of mice;[23] and head trauma could substantially increase expressions of STC1 in the rat brain.[19] Overall, STC1 should be released from brain tissues after acute brain injury. In line with a previous study, which showed a significant elevation of serum STC1 levels in patients with aneurysmal subarachnoid hemorrhage,[20] we found a substantial enhancement of serum STC1 levels after sTBI. In our

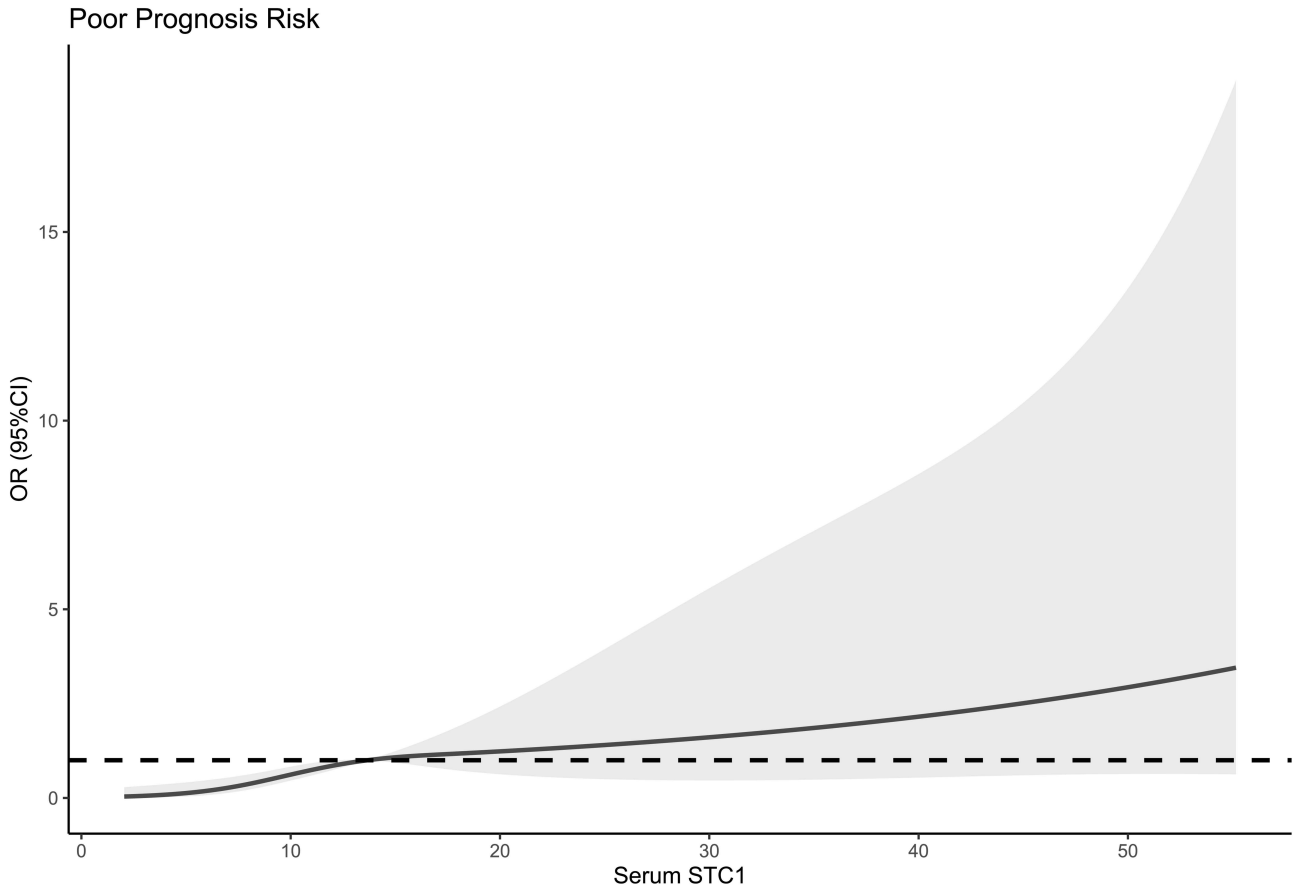

Figure 14 Restricted cubic spline demonstrating linear relation of serum stanniocalcin-1 levels to poor prognosis risk. Serum stanniocalcin-1 levels were linearly correlated with poor prognosis risk.
Abbreviations: STC1 indicates stanniocalcin-1; OR, odds ratio; 95% CI, 95% confidence interval.

study, patients' blood was collected from 1.0 to 13.4 hours after head trauma, with a median value of 5.7 hours. Thus, it is inferred that serum STC1 levels may be increased in early phase of acute brain injury. Theoretically, in consideration of its expressive ability in brain tissues after acute brain injury, the conceivable explanation is that STC1 in peripheral blood may be at least partially derived from damaged brain tissues.

A recent study demonstrated that serum STC1 levels were closely correlated with the severity and were highly associated with 1-year functional outcome, which was assessed via the Glasgow outcome scale after aneurysmal subarachnoid hemorrhage in humans.[20] In our study, GCS and Rotterdam CT classification were regarded as the two severity indicators, both of which were identified as the continuous and categorical variables. Using univariate analysis, serum STC1 levels were tightly correlated with trauma severity. Also, such a correlation was not changed when multivariate analysis was used. As for prognostic analysis, death, overall survival, GOSE scores and poor prognosis at 180 days after sTBI were considered as the four prognostic parameters. Serum STC1 levels were proved to be independently associated with the preceding parameters. Also, linear relations were found between serum STC1 levels and prognostic parameters. And, no interactions were found here. Noteworthily, prediction model integrating serum STC1 levels, GCS scores and Rotterdam CT scores, displayed extraordinarily efficiently discriminatory ability for death and poor prognosis after sTBI. Thus, these results may offer sufficient evidence to support the hypothesis that serum STC1 might be a useful biochemical maker in prognostication of sTBI.

There are still several strengths and weaknesses in the current study. The strengths are that (1) to the best of our knowledge, serum STC1 levels were determined in sTBI patients for the first time, and therefore some interesting results were found, which showed that serum STC1 may be a useful prognostic biomarker of sTBI;

Subgroup	Total	OR(95% CI)	P	P interaction
Age				0.328
≥ 60 years	13	0.988 (0.758-1.289)	0.934	
< 60 years	91	1.073 (1.024-1.124)	0.003	
Gender				0.187
Male	58	1.116 (1.005-1.240)	0.041	
Female	46	1.092 (0.974-1.223)	0.131	
Hypertension				0.454
Yes	18	1.190 (0.957-1.478)	0.117	
No	86	1.064 (1.015-1.115)	0.011	
Diabetes mellitus				0.089
Yes	13	2.789 (0.456-9.762)	0.267	
No	91	1.063 (1.017-1.111)	0.007	
Dyslipidemia				0.187
Yes	22	1.017 (0.958-1.079)	0.582	
No	82	1.086 (1.007-1.172)	0.033	
Cigarette smoking				0.299
Yes	30	1.053 (0.851-1.302)	0.638	
No	74	1.069 (1.018-1.122)	0.008	
Alcohol drinking				0.102
Yes	36	1.065 (1.012-1.120)	0.015	
No	68	1.144 (1.018-1.286)	0.024	

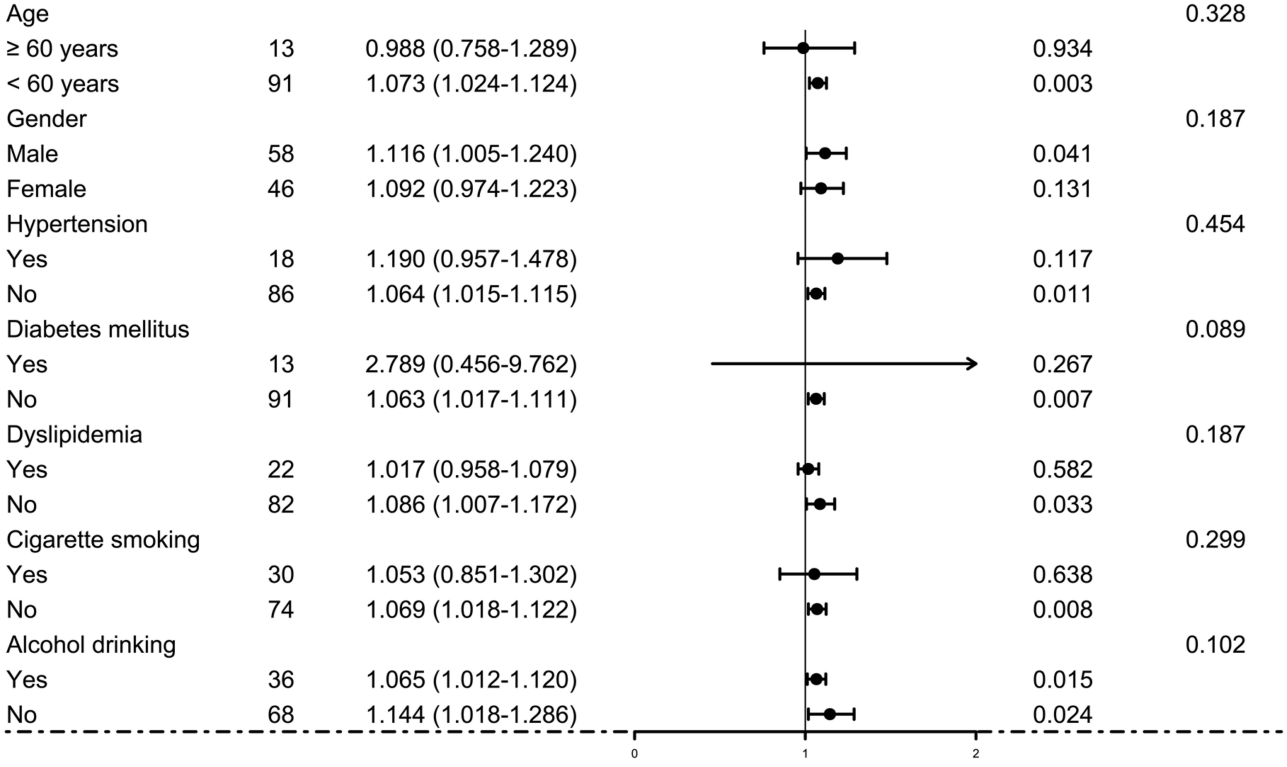

Figure 15 Subgroup analysis verifying interaction between serum stanniocalcin-1 levels and other variables for predicting poor prognosis. No interactions were found between serum stanniocalcin-1 levels and other variables, such as age, gender and hypertension (all P interaction >0.05).
Abbreviations: OR, means odds ratio; 95% CI, 95% confidence interval.

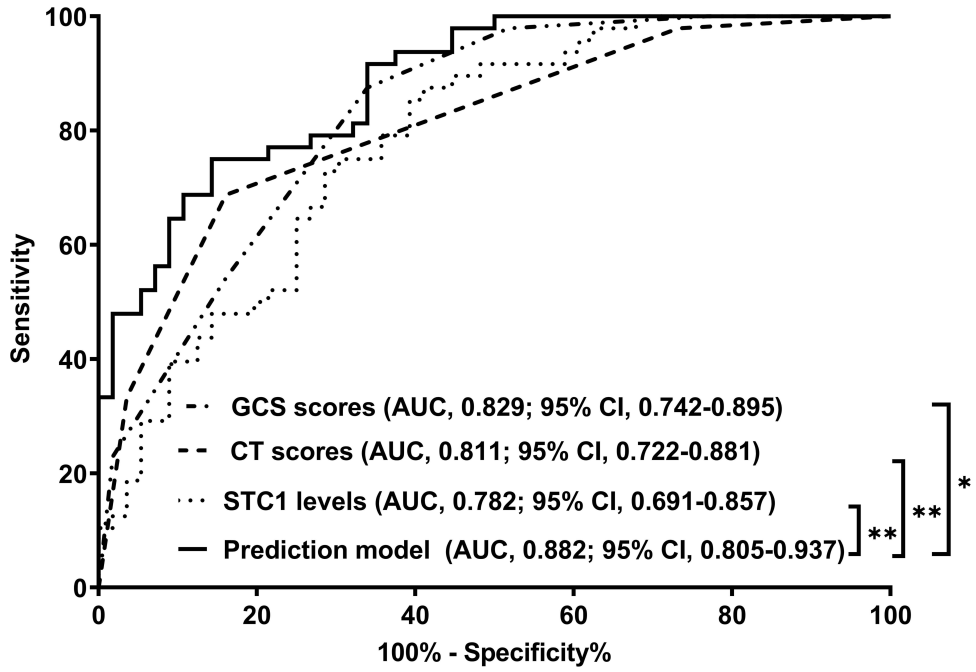

Figure 16 Receiver operating characteristic curves showing comparisons of various variables for prognostic prediction at 180 days after severe traumatic brain injury. Serum stanniocalcin-1 levels showed similar prognostic predictive ability, as opposed to Glasgow coma scale scores and Rotterdam computed tomography scale scores (both P>0.05). Prediction model integrating serum stanniocalcin-1 levels, Glasgow coma scale scores and Rotterdam computed tomography scale scores, had significantly higher prognostic predictive capability than any one of them. *P<0.05, **P<0.01.
Abbreviations: STC1 indicates stanniocalcin-1; GCS, Glasgow coma scale; CT, computed tomography; AUC, area under curve; 95% CI, 95% confidence interval.

(2) multiple variables, including mortality, overall survival, GOSE scores, poor prognosis and severity indicators, were applied to reflect severity and prognosis of sTBI; and (3) all correlations or associations were verified sequentially using univariate analysis and multivariate analysis. Thus, the conclusions may be comparatively scientific and believably acceptable. The weaknesses are that (1) STC1 can be generated from a diversity spectrum of tissues or cells, including cardiomyocytes, peripheral blood cells, culprit coronary plaques, brain, intestines, uterus, ovaries and placenta.[25–29] To the best of our knowledge, there is a paucity of data regarding relationships between STC1 and some chronic diseases, such as hypertension, diabetes mellitus and dyslipidemia; as well as between STCI and some specific medications, such as antihypertensive use, hypoglycemic or insulin use, and statin use. However, its correlations with those conditions may exist. In our study, controls were not complicated with those chronic diseases and did not take those medications. Maybe, another group of controls with those conditions should be enrolled in future and therefore correlations of STC1 with chronic diseases and specific medications could be uncovered. (2) sTBI patients were studied in this study, so the conclusions can not be extended to patients with mild-moderate TBI. (3) no significant correlations were revealed between serum STC1 levels and blood glucose levels using univariate analysis in the current study. Admittedly, in order to investigate whether STC1 could affect glucose metabolism, a next experiment or a large cohort study may be warranted. And, (4) this study contained 104 patients and therefore the conclusions warrant to be validated in a larger cohort study.

Conclusions

The noteworthy findings of the current study are that there is a significant elevation of serum STC1 levels after sTBI, which is independently correlated with the two severity indicators, namely GCS scores and Rotterdam CT scores, and is independently associated with 180-day mortality, overall survival, GOSE scores and poor prognosis after sTBI, as well as that prediction model, which integrates serum STC1 levels, GCS scores and Rotterdam CT scores, has high discriminatory efficiency for the risk of death and poor prognosis at 180 days following sTBI. The preceding results are strongly supportive of the assumption that serum STC1 may be take possession of significant prognostic predictive ability in sTBI and could serve as a prognostic biomarker in clinical work of sTBI.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due for they are personal data but are available from the corresponding author on reasonable request.

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Disclosure

The authors declare that they have no competing interests in this work.

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