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Evaluation of serum pannexin-1 as a prognostic biomarker for traumatic brain injury

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ABSTRACT

Background: Pannexin-1 is a type of hexameric plasma membrane channel-forming proteins, and plays a significant role in brain injury. We investigated the potential prognostic value of pannexin-1 in traumatic brain injury.

Methods: A single peripheral blood sample in 112 patients with severe traumatic brain injury and 112 controls was prospectively collected for subsequent measurement of serum pannexin-1. Clinical follow-up was performed at 6 months. An unfavorable outcome was defined as Glasgow Outcome Scale score of 1–3.

Results: The patients showed markedly higher serum pannexin-1 concentrations than the controls. Among the patients, pannexin-1 concentrations were significantly and negatively correlated with Glasgow coma scale scores. On receiver operating characteristic curve analysis, the predictive value in terms of area under the curve was substantially high for serum pannexin-1 as a predictor for both 6-month mortality and unfavorable outcome. Regression analyses confirmed that there was an increased risk of either 6-month mortality, overall survival or unfavorable outcome associated with serum pannexin-1 concentrations after adjusting for possible confounders.

Conclusions: Serum pannexin-1 may represent a potential prognostic biomarker for head trauma.

1. Introduction

Traumatic brain injury (TBI), particularly severe TBI, is one of the most common causes of death and adult disability worldwide [1–5]. After TBI, there are two types of injury in the neural tissue. One is the primary injury, which refers to the initial physical forces applied to the brain at the moment of the impact. The other is the secondary injury, which develops over a period of h or days later, involving some complicated pathophysiological changes, including neuroinflammatory response, free radical generation and apoptosis [6–9]. An early risk assessment with estimate of the severity of disease and prognosis is crucial for optimized care and allocation of healthcare resources to improve outcome. Very often, TBI severity and prognosis are determined via Glasgow coma scale (GCS) [10–12]. In recent decades, discovery of novel biomarkers has attracted the interests of researchers for identifying subjects at risk of poor prognosis [13–15].

Pannexin-1 is a member of the pannexin family, which includes three transmembrane channel proteins with a conserved pattern of cysteines [16]. Pannexin-1 channels locate on the cell membrane and releases adenosine triphosphate, nucleotides and molecules up to 1 kDa into the extracellular space, when activated. Activation of pannexin-1 channels can proceed by various mechanisms, including mechanostretch, a1-adrenergic/histamine stimulation, oxygen-glucose deprivation and caspase-mediated cleavage of the C-terminal portion, which results in an irreversible opening of the channel pore [17–19]. A growing body of evidence suggests that pannexin-1 channels contribute to the progression of pathophysiology in many diseases, such as Crohn's disease, AIDS, melanoma and chronic intestinal inflammation [20–23]. Pannexin-1 can be expressed on animal or human neuronal and glial cells [24]. Its expression is up-regulated in response to hypoxia, isotonic stress and ischemia [25–28]. Pannexin-1 is involved in pathophysiological processes of epilepsy, spinal cord injury and stroke [29–32]. Recently, it is found that inhibition of pannexin-1 significantly alleviated neuronal apoptosis and degeneration in rats with intracerebral hemorrhage, as well as obviously lessened brain inflammatory response and neuronal apoptosis after subarachnoid hemorrhage in rats [33,34], implying that pannexin-1 may contribute to brain injury. However, circulating pannexin-1 concentrations are not investigated in head trauma patients.

Abbreviations: GCS, Glasgow coma scale; GOS, Glasgow outcome scale

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2. Materials and methods

2.1. Design and subjects

The study design was a prospective and observational study. All consecutive patients with isolated and severe TBI from The Central Hospital of Wenzhou City, China, between May 2014 and May 2017 were recruited to participate in the study. Severe TBI was defined as postresuscitation Glasgow Coma Scale (GCS) score < 9. Isolated TBI referred to a non-head abbreviated injury scale score < 3. Patients were included if they were admitted to the emergency department within 6 h post-traumatically. Non-selection criteria included < 18 y a history of head trauma, previous neurological diseases including ischemic or hemorrhagic stroke, a history of antiplatelet medication or anticoagulant usage, an infection within recent 4 weeks, and presence of other systemic diseases, including uremia, liver cirrhosis, malignancy and chronic heart or lung disease. A group of healthy individuals were assigned to the healthy control group. According to the Declaration of Helsinki, this study was approved by the ethics committee at our hospital and written informed consent was obtained from the controls or legal representatives of the patients before implementation.

2.2. Variables recorded

Demographic, laboratory and clinical data, including sex, age, arterial blood pressure, blood oxygen saturation, blood glucose concentrations and pupillary reactivity, were recorded on admission. We assessed trauma severity by using the postresuscitation GCS score. All head computerized tomography (CT) examinations were carried out on accordance with the protocol of radiological department. Investigators were inaccessible to clinical information. On initial CT scan, we recorded the radiological parameters as follows: abnormal cisterns, midline shift > 5 mm, subarachnoid hemorrhage and Marshall CT classification [35]. Clinical follow-up lasted 6 months after head trauma. The functional outcome was assessed using Glasgow outcome scale (GOS) scores [36], which was dichotomized into poor outcome (GOS score 1 to 3) and good outcome (GOS score 4 to 5).

2.3. Measurements

Blood samples were collected in tubes with separator gel to obtain serum from patients with severe TBI on admission and controls at study entry to gauge concentrations of pannexin-1. After coagulation during 10 min at room temperature, serum was acquired by centrifugation at 1000 x *g* for 15 min. The samples were aliquoted and frozen at −80 °C until assayed. All determinations were completed in batches every 3 months by the same laboratory technician blinded to all clinical data. We quantified serum pannexin-1 concentrations in duplicates with commercially available enzyme-linked immunosorbent assay kits (CUSABIO, Wuhan, China) following the manufacturer's protocol. The mean values of two measurements were utilized for analyses.

2.4. Statistical methods

The results were reported as counts (percentages) for categorical variables and as medians (interquartile ranges, IQRs) for continuous variables, which were all non-normally distributed in this study. The Mann–Whitney *U* test and χ^2 test were utilized to compare intergroup differences of categorical variables and continuous variables respectively. Bivariate correlation between serum pannexin-1 concentrations and GCS scores were analyzed using Spearman's rank correlation test. Binary logistic regression was conducted for adjustments of potential confounders and for assessing predictors of poor prognosis. Univariate logistic regression models were configured and those variables found to be predictors were then analyzed with multivariate model. The odds ratio (OR) values and 95% confidence intervals (CIs) were estimated. A multivariate Cox's proportional hazard model was established to identify predictors of 6-month overall survival. The hazard ratio (HR) values and 95% CI values were calculated. Receiver operating characteristic (ROC) curves were configured to determine cutoff values for optimal predictive sensitivities and specificities. The area under curves (AUCs) and 95% CI were calculated. SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis and a $P < .05$ were considered significant. Graphics were done with GraphPad Prism Software version 5.00. ROC analysis was performed using MedCalc 9.6.4.0.

3. Results

3.1. Study population characteristics

During the study period, we recruited a total of 143 isolated and severe TBI, who were admitted to the emergency department within 6 h after head trauma. In accordance with exclusion criteria, we excluded twenty-seven patients, among whom, 2 patients had < 18 years of age, 3 patients experienced head trauma previously, 10 patients suffered from neurological diseases in the past, 5 patients had a history of antiplatelet medication or anticoagulant usage, 3 patients were infected within recent 4 weeks and 4 patients had presence of other systemic diseases. In addition, we excluded 4 patients with loss to follow-up (2 cases), an unavailable blood sample (1 case) and refusal to participation (1 case). Eventually, 112 patients were assessed. Also, 112 controls were enrolled. By statistical analysis, there were no statistical differences in age and gender percentage between controls and patients.

Among this group of patients, including 67 males and 45 females, age ranged from 18 to 76 y (median, 45 y; IQR, 33–60 y). In terms of clinical severity, GCS scores ranged from 3 to 8, with a median value of 5 and an IQR of 4 to 7. Also, via the initial radiological examination, sixty-two patients had Marshall CT classification 5 or 6, abnormal cisterns occurred in 54 patients, midline shift > 5 mm was found in 56 patients and traumatic subarachnoid hemorrhage appeared in 63 patients. In total, 59 patients underwent intracranial operation within first 24 h after trauma. Patients were admitted at the median time of 1.9 h (range, 0.5–6.0 h; IQR, 1.1–2.5 h) following trauma. Blood samples were collected from posttraumatic 1.0 to 8.0 h (median, 2.9 h; IQR, 2.4–3.6 h). As regards arterial blood pressure, the median systolic and diastolic arterial blood were 124 mmHg (range, 52–182 mmHg; IQR, 98–147 mmHg) and 77 mmHg (range, 30–110 mmHg; IQR, 56–91 mmHg) respectively. With respect to laboratory test, there were 8.0×10^9/l at the median white blood cell count (range, 3.8–15.8 × 10^9/l; IQR, 5.6–11.0 × 10^9/l), 8.8 mmol/l at the median blood glucose concentrations (range, 2.8–25.6 mmol/l; IQR, 7.6–11.6 mmol/l) and 9.3 mg/l at the median serum C-reactive protein concentrations (range, 3.1–22.9 mg/l; IQR, 6.9–12.3 mg/l). During 6-month clinical follow-up, a total of 33 patients (29.5%) were deceased and the percentage of patients experiencing an unfavorable outcome was 49.1% (55/112).

3.2. Serum pannexin-1 concentrations and its correlation analysis

In Fig. 1, serum pannexin-1 concentrations of the controls ranged from 0.8 to 4.0 mg/ml and its median value was 2.3 mg/ml, with an IQR of 1.4 to 2.9 mg/ml; pannexin-1 concentrations in the patients had a range of 2.7 to 17.4 mg/ml, with its median value being 7.5 mg/ml and its IQR value ranging from 5.6 to 9.1 mg/ml. By statistical analysis, pannexin-1 concentrations were substantially higher in the patients than in the controls ($P < .001$). In the current study, GCS scores were calculated to assess the clinical severity of traumatized brain injury. In Fig. 2, bivariate correlation analysis showed that serum pannexin-1 concentrations were strongly and negatively correlated with GCS scores ($r = -0.554$, $P < .001$), indicating that serum pannexin-1 concentrations might reflect trauma severity.

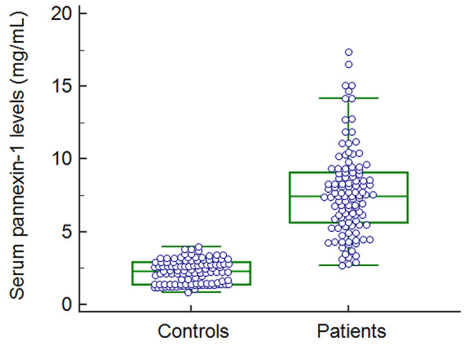

Fig. 1. Comparison of serum pannexin-1 concentrations between healthy controls and head trauma patients. Using the Mann–Whitney *U* test, serum pannexin-1 concentrations were statistically significantly higher in the patients than in the controls ($P < .001$).

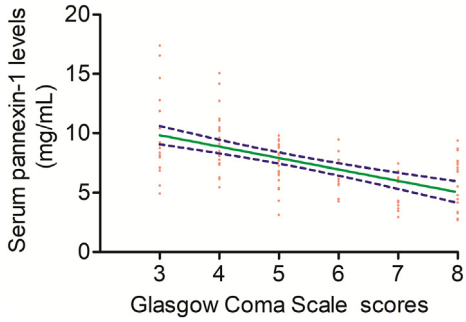

Fig. 2. Relationship between serum pannexin-1 concentrations and Glasgow Coma Scale score in patients with traumatic brain injury. Using Spearman correlation coefficient, serum pannexin-1 concentrations were strongly and negatively correlated with Glasgow Coma Scale scores ($r = -0.554$, $P < .001$).

3.3. Mortality prediction

In Table 1, we used univariate analysis and thereby demonstrated that the dead patients within 6 months after head trauma had older age, lower GCS scores, a higher percentage of computerized tomography classification 5 or 6, initial abnormal cisterns, initial midline shift > 5 mm and initial traumatic subarachnoid hemorrhage, as well as higher blood glucose, serum C-reactive protein and pannexin-1 concentrations.

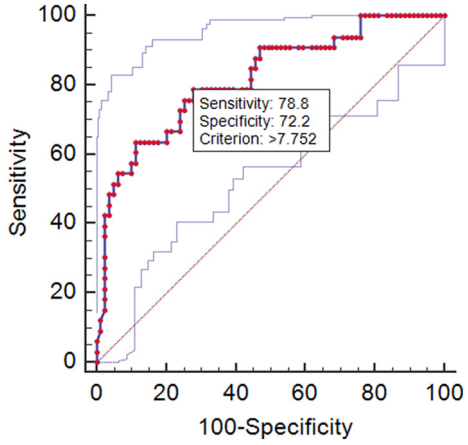

Fig. 3. Receiver operating characteristic curve of serum pannexin-1 concentrations for discriminating head trauma patients at risk of 6-month mortality. Under the receiver operating characteristic curve, an optimal cutoff value of pannexin-1 concentrations (7.75 mg/ml) was chosen, which discriminated patients at risk of 6-month death with 78.8% sensitivity and 72.2% specificity values with area under curve at 0.818 (95% confidence interval, 0.734–0.884).

Furthermore, the above-mentioned parameters verified to be significant in univariate analysis were incorporated into the binary logistic regression model and subsequently it was revealed that serum pannexin-1 (OR = 1.312, 95% CI = 1.012–1.700, $P = .041$) and GCS score (OR = 0.290, 95% CI = 0.178–0.465, $P < .001$) were the 2 independent predictors for 6-month mortality. In Fig. 3, under the ROC curve, an optimal cutoff value of pannexin-1 concentrations (7.75 mg/ml) was chosen, which discriminated patients at risk of 6-month death with 78.8% sensitivity and 72.2% specificity values with AUC at 0.818 (95% CI, 0.734–0.884).

3.4. Functional outcome prediction

As listed in Table 2, the univariate analysis demonstrated that older age, lower GCS scores, a higher percentage of computerized tomography classification 5 or 6, initial abnormal cisterns, initial midline shift > 5 mm and initial traumatic subarachnoid hemorrhage, as well as higher blood glucose, serum C-reactive protein and pannexin-1 concentrations were significantly associated with increasing risk of developing 6-month poor outcome. When those aforementioned significant

Table 1
The factors associated with 6-month mortality.

	Univariate analysis			Univariate logistic regression analysis		
	Non-survivors	Survivors	*P* value	Odds ratio	95% CI	*P* value
Sex (male/female)	23/10	44/35	NS	1.830	0.770–4.345	NS
Age (y)	54 (40–63)	41 (25–56)	0.021	1.028	1.005–1.052	0.019
Glasgow coma scale score	3 (3–4)	6 (5–7)	< 0.001	0.176	0.085–0.366	< 0.001
Computerized tomography classification 5 or 6	26 (78.8%)	36 (45.6%)	0.001	4.437	1.725–11.412	0.002
Initial abnormal cisterns	24 (72.7%)	30 (38.0%)	0.001	4.356	1.787–10.614	0.001
Initial midline shift > 5 mm	22 (66.7%)	34 (43.0%)	0.023	2.647	1.132–6.192	0.025
Initial traumatic subarachnoid hemorrhage	24 (72.7%)	39 (49.4%)	0.023	2.735	1.130–6.620	0.026
Intracranial surgery in first 24 h	21(63.6%)	38 (48.1%)	NS	1.888	0.819–4.353	NS
Time between trauma and admission (h)	1.8 (1.2–2.5)	1.9 (1.1–2.4)	NS	0.893	0.622–1.284	NS
Blood-collecting time (h)	3.1 (2.6–4.0)	2.8 (2.4–3.5)	NS	0.957	0.792–1.156	NS
Systolic arterial pressure (mmHg)	123 (90–157)	124 (97–145)	NS	1.001	0.989–1.013	NS
Diastolic arterial pressure (mmHg)	75 (58–92)	78 (54–89)	NS	1.005	0.985–1.025	NS
Blood white blood cell ($\times 10^9$/l)	9.5 (4.4–12.5)	7.5 (5.8–9.7)	NS	1.098	0.965–1.249	NS
Blood glucose level (mmol/l)	10.1 (8.0–14.2)	8.5 (7.6–10.1)	0.018	1.157	1.033–1.296	0.012
Serum C-reactive protein (mg/l)	11.1 (7.4–14.5)	8.6 (6.9–11.3)	0.012	1.156	1.038–1.288	0.008
Serum pannexin-1 (mg/ml)	9.6 (8.1–11.9)	6.8 (5.3–8.2)	< 0.001	1.629	1.312–2.024	< 0.001

The results were reported as counts (percentages) for categorical variables and as medians (interquartile ranges) for continuous variables. Comparisons were done by the Mann–Whitney *U* test or χ^2 test as appropriate. 95%CI denotes 95% confidence interval.

Table 2
The factors associated with 6-month poor outcome.

	Univariate analysis			Univariate logistic regression analysis		
	Poor outcome	Good outcome	*P* value	Odds ratio	95% CI	*P* value
Sex (male/female)	34/21	33/24	NS	1.177	0.553–2.509	NS
Age (y)	45 (38–63)	39 (23–56)	0.016	1.031	1.005–1.058	0.018
Glasgow coma scale score	4 (3–5)	7 (5–8)	< 0.001	0.270	0.168–0.433	< 0.001
Computerized tomography classification 5 or 6	38 (69.1%)	24 (42.1%)	0.004	3.074	1.413–6.684	0.005
Initial abnormal cisterns	35 (63.6%)	19 (33.3%)	0.001	3.500	1.608–7.619	0.002
Initial midline shift > 5 mm	33 (60.0%)	23 (40.4%)	0.038	2.217	1.042–4.721	0.039
Initial traumatic subarachnoid hemorrhage	37 (67.3%)	26 (45.6%)	0.021	2.451	1.138–5.280	0.022
Intracranial surgery in first 24 h	34 (61.8%)	25 (43.9%)	NS	0.057	0.974–4.408	NS
Time between trauma and admission (h)	1.9 (1.3–2.6)	2.0 (0.9–2.5)	NS	0.752	0.536–1.055	NS
Blood-collecting time (h)	3.0 (2.4–4.0)	2.8 (2.3–3.3)	NS	1.049	0.900–1.224	NS
Systolic arterial pressure (mmHg)	119 (83–150)	126 (102–147)	NS	0.992	0.980–1.003	NS
Diastolic arterial pressure (mmHg)	70 (52–96)	80 (62–87)	NS	0.992	0.974–1.010	NS
Blood white blood cell ($\times 10^9$/l)	6.2 (4.4–11.4)	8.1 (6.3–10.6)	NS	0.940	0.834–1.059	NS
Blood glucose (mmol/l)	9.9 (7.8–13.4)	8.3 (7.6–9.7)	0.018	1.128	1.021–1.204	0.042
Serum C-reactive protein (mg/l)	10.8 (7.1–14.3)	8.6 (6.6–11.2)	0.025	1.135	1.025–1.257	0.015
Serum pannexin-1 (mg/ml)	9.0 (7.4–11.1)	6.3 (4.4–7.6)	< 0.001	1.964	1.498–2.576	< 0.001

The results were reported as counts (percentages) for categorical variables and as medians (interquartile ranges) for continuous variables. Comparisons were done by the Mann–Whitney U test or χ^2 test as appropriate. 95%CI denotes 95% confidence interval.

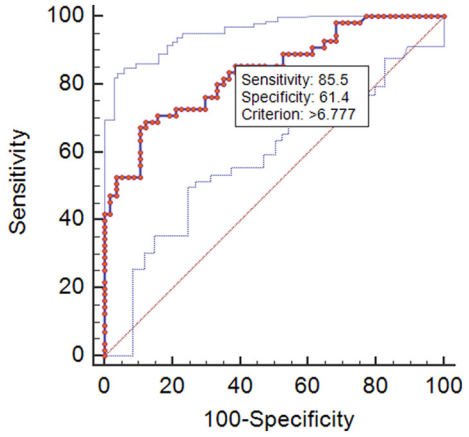

Fig. 4. Receiver operating characteristic curve of serum pannexin-1 concentrations for predicting 6-month poor outcome in head trauma patients. A receiver operating characteristic curve estimated an area under curve of 0.837 (95% confidence interval, 0.755–0.900) and selected a suitable cutoff value of serum pannexin-1 concentration (6.78 mg/ml) as an indicator for predicting 6-month poor outcome, which generated a sensitivity value of 85.5% and a specificity value of 61.4%.

parameters were further analyzed in the multivariate logistic model, serum pannexin-1 and GCS score were found to independently discriminate the development of 6-month poor outcome with OR values of 1.570 (95% CI = 1.128–2.187, *P* = .008) and 0.375 (95% CI = 0.229–0.614, *P* < .001) respectively. Just as depicted in Fig. 4, a ROC curve estimated an AUC of 0.837 (95% CI, 0.755–0.900) and selected a suitable cutoff value of serum pannexin-1 concentration (6.78 mg/ml) as an indicator for predicting 6-month poor outcome, which generated a sensitivity value of 85.5% and a specificity value of 61.4%.

3.5. Survival analysis

Table 3 shows that older age, lower GCS scores, a higher percentage of computerized tomography classification 5 or 6, initial abnormal cisterns, initial midline shift > 5 mm and initial traumatic subarachnoid hemorrhage, higher blood glucose, serum C-reactive protein and pannexin-1 concentrations were strongly related to the risk of shorter 6-month overall survival time. When the preceding intimately correlative variables were further incorporated in the multivariate logistic model, serum pannexin-1 and GCS score emerged as the 2 independent predictors for 6-month overall survival with OR values of 1.116 (95% CI = 1.007–1.238, *P* = .037) and 0.314 (95% CI = 0.196–0.503, *P* < .001) respectively.

Table 3
The factors associated with 6-month overall survival.

	Hazard ratio	95% confidence interval	*P* value
Sex (male/female)	1.659	0.790–3.487	NS
Age (y)	1.023	1.002–1.044	0.031
Glasgow coma scale score	0.288	0.185–0.448	< 0.001
Computerized tomography classification 5 or 6	3.591	1.558–8.277	0.003
Initial abnormal cisterns	3.303	1.534–7.111	0.002
Initial midline shift > 5 mm	2.160	1.047–4.455	0.037
Initial traumatic subarachnoid hemorrhage	2.234	1.038–4.808	0.040
Intracranial surgery in first 24 h	1.768	0.870–3.594	NS
Time between trauma and admission (h)	0.902	0.661–1.229	NS
Blood-collecting time (h)	0.998	0.786–1.268	NS
Systolic arterial pressure (mmHg)	1.005	0.994–1.016	NS
Diastolic arterial pressure (mmHg)	1.006	0.990–1.023	NS
Blood white blood cell ($\times 10^9$/l)	1.095	0.979–1.226	NS
Blood glucose (mmol/l)	1.159	1.059–1.269	0.001
Serum C-reactive protein (mg/l)	1.146	1.054–1.246	0.001
Serum pannexin-1 (mg/ml)	1.298	1.182–1.426	< 0.001

The results were produced using univariate Cox's proportional hazard analysis.

4. Discussion

The objective of the current study was to investigate the relationship between the serum pannexin-1 concentration and trauma severity in addition to clinical outcomes of patients with TBI. The results of the current study show that TBI patients had the higher concentrations of serum pannexin-1 compared to the control group. According to the results of this study, there was a significant correlation between the pannexin-1 concentrations and the degree of brain injury in terms of GCS scores. Also, serum pannexin-1 concentrations were markedly higher in the patients with death or poor prognosis at 6 months after trauma than the alive or those with good prognosis. Alternatively, a

multivariate logistic regression model identified serum pannexin-1 as an independent predictor for long-term clinical outcomes, namely, 6-month mortality, overall survival and poor outcome (defined as Glasgow outcome scale score of 1–3). On the other hand, ROC curve actually verified its high predictive performance for long-term clinical outcomes. Taken together, the preceding data are supportive of the notion that pannexin-1 concentrations might be intimately linked to disease severity and long-term clinical outcomes after TBI, substantializing pannexin-1 as a promising prognostic biomarker for TBI.

Pannexin genes belong to the gap junction family because their structural features are similar to those of gap junction proteins [16]. Pannexin genes code three types of proteins: pannexin-1, pannexin-2 and pannexin-3. Pannexin-1 and pannexin-2 are broadly found in the central nervous system, but pannexin-3 not [17–19]. Pannexin-1 is relatively specifically expressed in neurons and astrocytes, where it is a component of the large pore ion channel [24]. ATP, $Ca2+$, arachidonic acid, glutamate and other signaling molecules are released through pannexin-1 channels. Pannexin-1 could utilize specific mechanism to facilitate the release of signaling molecules. For instance, it activates infammasome for the release of pro-inflammatory cytokines, such as interleukin-1 β [25–28]. Recent studies in the central nervous system have suggested the pannexin-1 channels is important for certain physiological functions, for instance, synaptic plasticity and learning and its abnormalities account for several pathological processes (e.g., ischemia, tumorigenesis, epilepsy) [29–32]. A recent report [37] has shown that pannexin-1 channel could affect kainic acid-induced seizure activity by using a pannexin-1-knockout mouse model. Thus, although the current study found the increased serum pannexin-1 concentrations in a group of TBI patients, its functions warrant to be studied in future. However, an interesting finding in this study was that serum pannexin-1 concentrations appeared to be highly associated with GCS scores. Seemingly, serum pannexin-1 concentrations could reflect the trauma severity, because the current study enrolled a total of 112 patients and thereby had enough statistical power to support the conclusion. In accordance with this sort of association, it is suggested that pannexin-1 should be related to secondary brain injury after TBI.

In general, GOS score of 1–3 refers to an unfavorable functional outcome in previous reports [14,15]. We also utilized such a definition to assess functional outcome in our study. GCS score is a common determinant for assessing prognosis of TBI [10–12]. In the current study, besides GCS score, serum pannexin-1 emerged as an independent predictor for 6-month mortality, overall survival and unfavorable outcome. Of note, its high prognostic predictive value was validated in a ROC curve showing that serum pannexin-1 concentrations on admission could obviously predict long-term unfavorable outcome and mortality. In summary, the determination of pannexin-1 in the serum of head trauma patients on admission provides the opportunity to discriminate TBI patients at risk of 6-month bad outcome.

5. Conclusions

The current study verified that high serum concentrations of pannexin-1 are closely associated with head trauma severity, and serum pannexin-1 independently predicts long-term clinical outcomes of TBI. In addition, serum pannexin-1 shows a high discriminatory ability for poor prognosis of patients with TBI. The results indicate that serum pannexin-1 can represent a potential prognostic biomarker for head trauma.

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