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Prognostic significance of serum translocator protein in patients with traumatic brain injury

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ABSTRACT

Background: Translocator protein (TP) is related to inflammation and is involved in brain injury. The objective of this study was to ascertain whether serum TP concentrations are associated with the severity and prognosis of traumatic brain injury (TBI).

Methods: We quantified the serum concentrations of TP in 106 healthy controls and 106 patients with severe TBI. Recorded prognostic variables included acute lung injury, acute traumatic coagulopathy, progressive hemorrhagic injury, posttraumatic cerebral infarction, 6-month mortality and 6-month poor outcome (Glasgow Outcome Scale score of 1–3). Trauma severity was assessed by Glasgow coma scale (GCS) score. Extent of inflammatory response was indicated by serum interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a) and C-reactive protein (CRP) concentrations.

Results: Patients had significantly higher serum TP concentrations than controls. Among patients, serum TP concentrations strongly and independently correlated with GCS score and serum IL-6, TNF-a and CRP concentrations. Serum TP was identified as an independent predictor for the preceding prognostic variables, its prognostic predictive ability was similar to that of GCS score and it also significantly improved prognostic predictive ability of GCS score.

Conclusion: Serum TP may be intimately linked with in inflammation, disease progression and poor prognosis in TBI patients.

1. Introduction

Traumatic brain injury (TBI) is one of the commonest traumatic forms characterized by a high percentage of mortality, physical disability and impaired quality of life [1–3]. Brain injury from external force provokes local and even systemic inflammatory response, which are mediated by, or result in, the release of various cytokines, including tumor necrosis factor (TNF-a), interleukin-6 (IL-6) and C-reactive protein (CRP) [4–8]. These inflammatory cytokines appear to play integral roles in the onset of post-traumatic disorders, such as, neurological deficits, acute lung injury (ALI), acute traumatic coagulopathy (ATC), progressive hemorrhagic injury (PHI) and posttraumatic cerebral infarction (PTCI) [9–19]. Translocator protein 18 kDa (TP), which is initially regarded as a peripheral benzodiazepine receptor, is now known as a receptor existing throughout the body and brain [20]. Under normal physiological status, TP concentrations are very low in the brain and restricted to glial cells. TP expression was demonstrated to coincide with the process of microglial activation, which is intimately linked with brain injury and neuroinflammation induced by TBI [21,22]. Recently, plasma TP has been reported to be associated with outcome in a small number of patients with acute ischemic stroke [23]. The accumulating data imply that TP might emerge as a biomarker for reflecting brain injury and neuroinflammation. However, the relationship between circulating TP concentrations and inflammation in addition to prognosis of TBI has yet to be studied.

Abbreviations: GCS, Glasgow coma scale; TBI, traumatic brain injury; ALI, Acute lung injury; ATC, acute traumatic coagulopathy; PHI, progressive hemorrhagic injury; PTCI, posttraumatic cerebral infarction; TP, translocator protein

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2. Methods

2.1. Study population

In this prospective, observational study, patients with non-penetrating severe TBI (postresuscitation Glasgow coma scale [GCS] score of ≤8) were medically evaluated at The CHC International Hospital (Cixi, China) from January 2014 to January 2017. We required that a non-head abbreviated injury scale score should be < 3, ≥2 head computed tomography (CT) scans should be done in the first 72 h after trauma and ≥ 4 head CT scans should be completed in the first week after injury. Exclusion criteria included age of < 18 y, admission time of > 6 h since trauma, infection within recent a month, previous head trauma, neurological diseases including ischemic or hemorrhagic stroke, use of antiplatelet or anticoagulant medication, or other prior systemic diseases including uremia, liver cirrhosis, malignancy, chronic heart or lung disease, diabetes mellitus and hypertension. Meantime, we chose some healthy individuals as controls. This study was approved by the Institutional Review Board of our hospital. Controls or patients' family provided written informed consent before enrollment in the present study.

2.2. Data collection

Demographic information and other comorbidities were examined upon admission. GCS score was calculated to estimate the degree of trauma severity. Abnormal cisterns, midline shift > 5 mm, traumatic subarachnoid hemorrhage and Marshall CT classification [24] were recorded on an initial CT scan. PHI and PTCI were diagnosed based on a follow-up CT scan. PHI was defined as any increase in size or number of the hemorrhagic lesion, including newly developed ones [25]. Diagnosis of PTCI was made according to the following criteria: (1) distinctly hypodense lesions within a defined cerebral vascular territory; (2) hypodense lesions located in boundary zones between the defined cerebral vascular territories or situated in the terminal zones of perforating arteries within the deep white matter [26]. ALI was diagnosed according to the international consensus criteria, which include acute onset, the ratio of partial pressure of arterial oxygen to fractional inspired oxygen ≤300, bilateral infiltrates on chest radiograph, and no clinical evidence of left arterial hypertension [27]. The recorded prognostic variables included 6-month mortality and 6-month unfavorable outcome (Glasgow outcome scale score of 1–3).

2.3. Determination

We collected venous blood from patients at admission and from controls at study entry. Coagulation test or blood routine test were assayed using the routine laboratory methods. ATC was defined as an activated partial thromboplastic time > 40 s and/or international normalized ratio > 1.2 and/or a platelet count < 120×10^9/l [28,29]. Venous blood was centrifuged at 3000 x *g* and subsequently, serum was stored at −80 °C until assayed. Serum concentrations of biomarkers were determined in accordance with the manufactures' instructions using commercially available enzyme-linked immunosorbent assay kits as follows: CRP, IL-6 and TNF-α (Cusabio Biotech); TP (Cloud-Clone Corp.). Because the minimum detectable concentration of TP for this kit is 0.127 ng/ml, a concentration of < 0.127 ng/ml was defined as zero. All measurements were in duplicate done in batches every 3 months by the same technician blinded to the clinical data. The mean values of two measurements were used for further analyses.

2.4. Statistical analysis

Softwares used in this study included SPSS 19.0 and MedCalc 9.6.4.0. Differences were considered to be significant at a $P < .05$. Qualitative data were shown as counts (percentage). Quantitative data are presented as median (interquartile range). To compare data between groups, the Mann-Whitney *U* test was performed for quantitative variables and the Pearson's chi-square test for qualitative variables. Spearman's correlation coefficient was used to analyze the correlation between two variables. Partial correlation analysis was conducted to adjust for the effects of confounding variables. We calculated the odds ratio (OR) and associated 95% confidence interval (CI) by a binary logistic regression to estimate the risk of ALI, ATC, PHI, PTCI, 6-month mortality and 6-month unfavorable outcome among subjects with higher TP concentrations versus those with lower TP concentrations after correction of some confounding factors, such as age, gender, traumatic subarachnoid hemorrhage, midline shift > 5 mm, Marshall CT classification and abnormal cisterns. A receiver operating characteristic curve (ROC) analysis and area under the ROC curve (AUC) were applied to express a measure of accuracy of TP for predicting patient outcomes. We also determined the cutoff value for optimally predicting a defined outcome status. The sensitivity and specificity were calculated using the proposed cutoffvalue. Moreover, a combined logistic-regression model was established and the additive benefit of serum TP concentrations to GCS scores was assessed. Intergroup comparisons of AUCs were carried out using Z test.

3. Results

3.1. Study population characteristics

In this study, we required that GCS score for TBI patients should be < 9, a non-head abbreviated injury scale score, < 3; ≥2 head CT scans, done in the first 72 h after trauma; at least four head CT scans, completed in the first week after injury. All head trauma patients were screened, and then only 145 patients were evaluated at first for consideration of enrollment in this study. According to exclusion criteria, 39 patients were excluded, among whom, 5 patients were aged at < 18 y, 8 patients were admitted at > 6 h post-traumatically, 2 patients suffered from infection within recent a month, 4 patients were head-traumatized previously, 7 patients experienced neurological diseases, 4 patients obtained antiplatelet or anticoagulant medication and 9 patients had other prior systemic diseases. In total, one hundred and six patients were recruited in the current study. Meanwhile, a total of 106 healthy controls were enrolled, among whom, 60 were males and 46 were females, with a median age of 37 y (range, 20–75 y; interquartile range, 28–50 y). And, they had similar gender percentage and age when compared with patients.

This group of patients (65 men and 41 women) with a median age of 35 y (range, 18–76 y; interquartile range, 24–52 y) had a median GCS score of 5 (range, 3–8; interquartile range, 3–6). A total of 49 patients (46.2%) had unreactive pupils. Radiological examination showed abnormal cisterns in 47 patients (44.3%), midline shift > 5 mm in 42 patients (39.6%), traumatic subarachnoid hemorrhage in 61 patients (57.6%) and Marshall CT classification 5 or 6 in 66 patients (62.3%). Those patients were admitted from 0.5 to 6.0 h after head trauma (median, 2.0 h; interquartile range, 1.0–3.0 h). Venous blood was collected from 1.0 to 7.0 h post-trauma (median, 3.3 h; interquartile range, 1.8–4.4 h). The patients underwent the first CT scan from 1.5 to 7.5 h after head trauma (median, 2.8 h; interquartile range, 2.0–3.5 h). Laboratory test showed that there were 16.6 mg/l at the median CRP concentrations (range, 3.5–33.8 mg/l; interquartile range, 10.1–20.6 mg/l), 9.4 pg/ml at the median IL-6 concentrations (range, 2.0–19.9 pg/ml; interquartile range, 5.3–12.3 pg/ml) and 8.6 pg/ml at the median TNF-a concentrations (range, 3.2–19.2 pg/ml; interquartile range, 5.9–13.6 pg/ml). Totally, 34 (32.1%), 42 (39.6%), 31 (29.2%) and 18 (17.0%) patients suffered from ALI, ATC, PHI and PTCI respectively. In addition, 52 patients (49.1%) experienced an unfavorable outcome at 6 months after head trauma and 30 patients (28.3%) were deceased within posttraumatic 6 month.

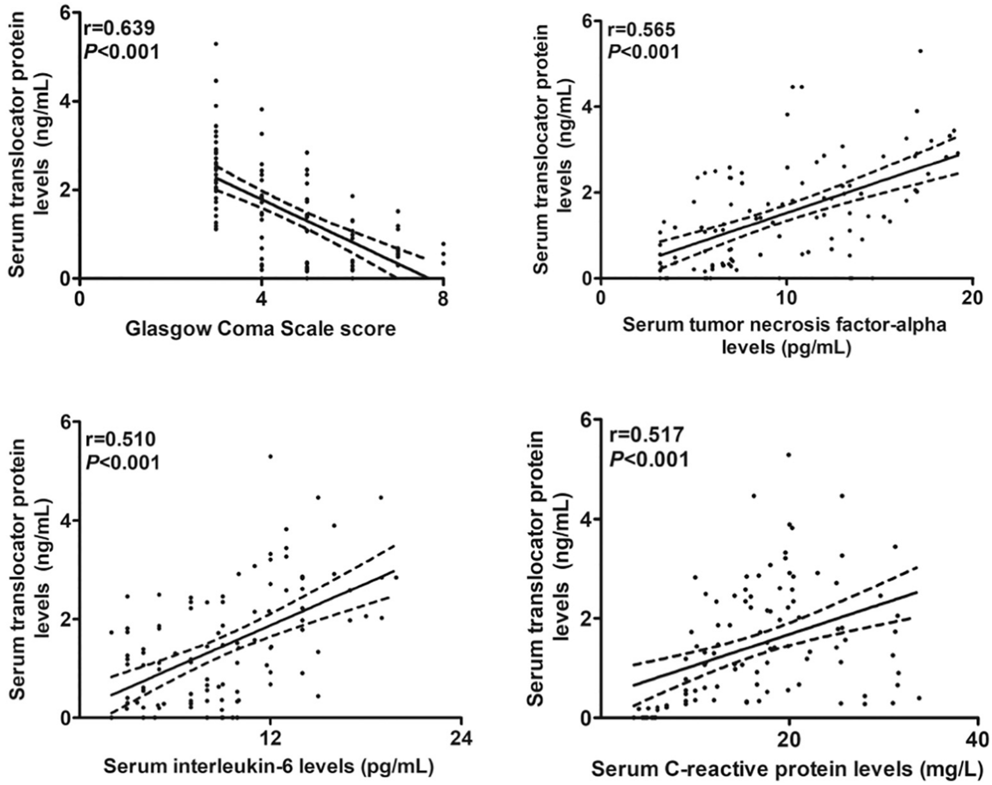

Fig. 1. Correlations of serum translocator protein concentrations with serum C-reactive protein, interleukin-6 and tumor necrosis factor-alpha concentrations in addition to Glasgow Coma Scale scores after severe traumatic brain injury.

3.2. Serum TP concentrations and other variables

Serum TP concentrations were undetectable in all controls (< 0.127 ng/ml) and were considered as 0. The distribution of TP titers in the patients ranged from 0 (undetectable in ten patients) to 5.29 ng/ml with a median of 1.32 ng/ml and an interquartile range of 0.39–2.34 ng/ml. Undoubtedly, serum TP concentrations were statistically significantly higher in patients than in controls ($P < .001$).

In order to investigate bivariate correlation, we used Spearman's correlation coefficient, and then it was found that serum TP concentrations significantly correlated with GCS score, as well as serum CRP, IL-6 and TNF-α concentrations ($r = -0.639$, 0.517, 0.510 and 0.565 respectively; all $P < .001$; Fig. 1). Moreover, using partial correlation analysis, after correction for some confounding factors, such as age, gender, unreactive pupils, abnormal cisterns, midline shift > 5 mm, traumatic subarachnoid hemorrhage, Marshall CT classification, admission time, blood-collecting time and time between trauma and first CT scan, statistically significant correlations still exist between serum TP concentrations and GCS score ($r = -0.573$, $P < .001$), between serum TP concentrations and CRP concentrations ($r = 0.399$, $P < .001$), between serum TP concentrations and IL-6 concentrations ($r = 0.423$, $P < .001$), as well as between serum TP concentrations and TNF-a concentrations ($r = 0.462$, $P < .001$).

3.3. Serum sST2 concentrations and prognosis

In Table 1, we utilized univariate logistic regression analysis to calculate OR values and 95% CI values, and the important finding was that serum TP concentrations were significantly associated with ALI, ATC, PHI, PTCI, 6-month mortality and 6-month unfavorable outcome; After adjusted by some confounding factors, such as age, gender, GCS scores, unreactive pupils, abnormal cisterns, midline shift > 5 mm, traumatic subarachnoid hemorrhage, Marshall CT classification, admission time, blood-collecting time and time between trauma and first CT scan, these associations were still statistically significant.

Table 1
Association of translocator protein levels with prognosis of head trauma.

	OR	95% CI	*P* value
Acute lung injury			
Univariate analysis	7.150	1.789–28.585	< 0.001
Multivariate analysis	2.924	1.643–5.202	0.003
Acute traumatic coagulopathy			
Univariate analysis	2.801	1.776–4.418	< 0.001
Multivariate analysis	3.114	1.769–5.481	0.001
Progressive hemorrhage injury			
Univariate analysis	2.718	1.710–4.320	< 0.001
Multivariate analysis	2.798	1.600–4.890	0.005
Posttraumatic cerebral infarction			
Univariate analysis	2.668	1.595–4.462	< 0.001
Multivariate analysis	2.504	1.427–4.394	0.001
6-month mortality			
Univariate analysis	2.553	1.627–4.007	< 0.001
Multivariate analysis	2.765	1.508–5.071	0.007
6-month unfavorable outcome			
Univariate analysis	3.633	2.163–6.103	< 0.001
Multivariate analysis	3.227	1.810–7.270	0.003

Using multivariate logistic regression analysis, some confounding factors (namely, age, gender, Glasgow coma scale score, unreactive pupils, abnormal cisterns, midline shift > 5 mm, traumatic subarachnoid hemorrhage, Marshall computerized tomography classification, admission time, blood-collecting time and time between trauma and the first computerized tomography scan) were corrected. Serum translocator protein concentration was identified as a categorical variable based its median value. Odds ratio and 95% confidence interval values were estimated.

In Fig. 2, serum TP concentrations discriminated patients at risk of ALI, ATC, PHI, PTCI, 6-month mortality or 6-month unfavorable outcome with a high AUC; moreover, we also determined the cutoff value for optimally predicting a defined outcome status; the sensitivity and specificity were calculated using the proposed cutoffvalue. In Table 2,

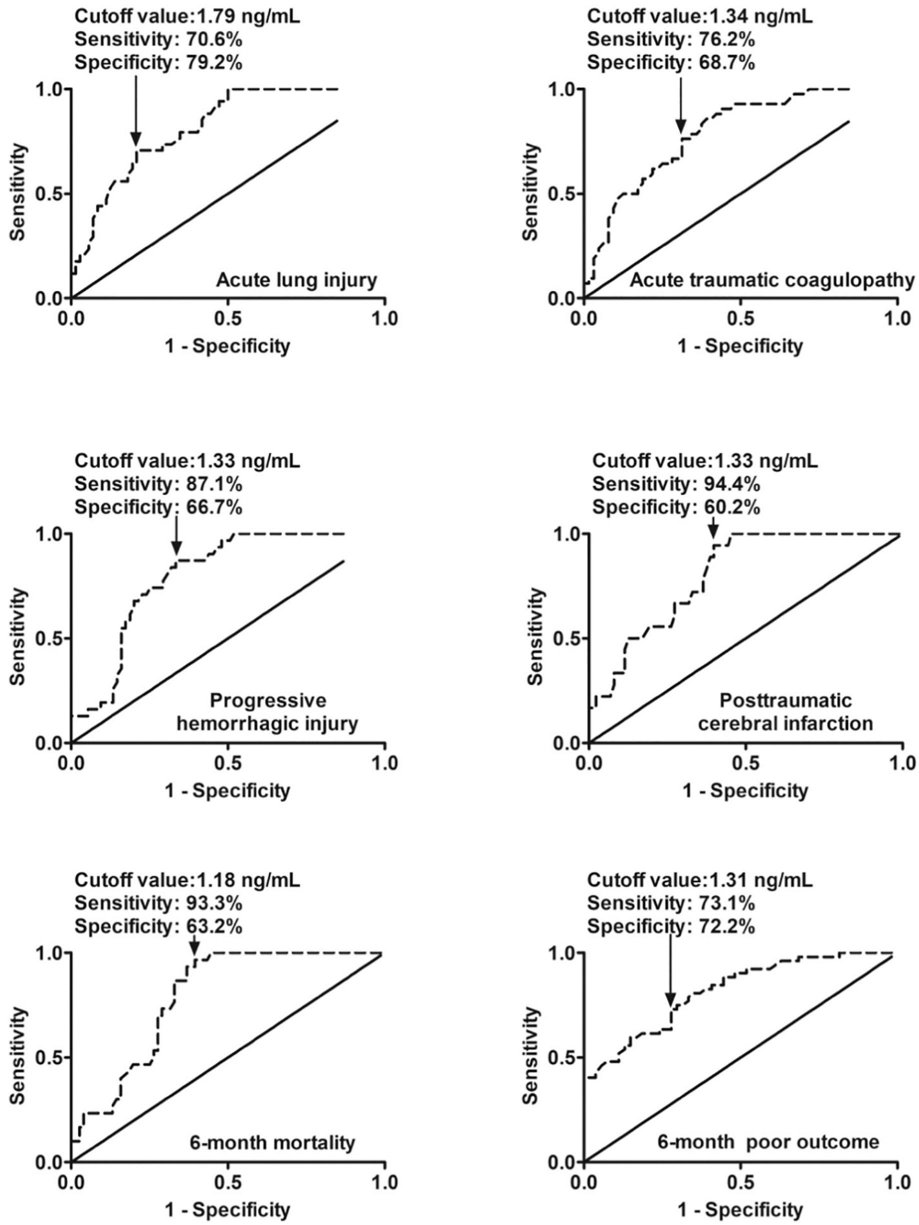

Fig. 2. Analysis of the distinguishing ability of serum translocator protein concentrations for differentiating patients at risk of acute lung injury, acute traumatic coagulopathy, progressive hemorrhagic injury, posttraumatic cerebral infarction, 6-month mortality and 6-month unfavorable outcome after severe traumatic brain injury using receiver operating characteristic curve.

for differentiating ALI, ATC, PHI, PTCI, 6-month mortality or 6-month unfavorable outcome, AUC of serum TP concentrations was in range of GCS score and also serum TP concentrations obviously improved the predictive ability of GCS score alone in terms of AUC.

4. Discussion

Increased serum TP concentrations within 6 h after head trauma was intimately and independently related to the appearance of ALI, PHI, ATC, PTCI, 6-month mortality and functional outcome at 6 months after TBI. It was accompanied by a good discriminative ability to predict the above-mentioned poor prognoses. Moreover, the initial TP concentrations were strongly correlated with GCS scores and serum CRP, IL-6 and TNF-a concentrations. It is suggested that TP should be linked to degree of trauma severity and such a biomarker might be associated with subsequent neuroinflammation which could be related to outcomes in this group of patients.

Following ischemic and hemorrhagic injury to the brain during the secondary brain injury after head trauma caused by an external force, a series of neuroinflammatory reactions ensue, including the activation of endogenous cells in central nervous system (namely, astrocytes, neurons, and microglia) and an influx of leukocytes [4–8]. It has been demonstrated that TP expression is up-regulated in microglia and in circulating macrophages leaking into the brain tissues under some pathological conditions, such as experimental TBI [30–33]. UP to now, TP has been chosen as a microglia marker because the majority of the TP-positive cells in injured brain are microglia [34]. Moreover, TP is expressed at low concentrations in the healthy brain but is remarkably up-regulated in response to injury and inflammation [21,22]. In other words, TP expression possessed the ability for reflecting inflammatory status after brain injury. The current study has found that increased serum TP concentrations were strongly correlated with serum IL-6, CRP and TNF-a concentrations using partial correlation analysis for adjusting other confounding factors, such as age, gender, midline shift,

Table 2
Discriminatory ability of translocator protein levels for prognosis of head trauma.

	AUC (95%CI)	*P* value
Acute lung injury		
GCS score alone	0.863 (0.783–0.922)	Reference
TP levels alone	0.818 (0.731–0.886)	NS
GCS score combined with TP	0.924 (0.856–0.967)	0.010
Acute traumatic coagulopathy		
GCS score alone	0.842 (0.758–0.905)	Reference
TP levels alone	0.792 (0.702–0.865)	NS
GCS score combined with TP	0.923 (0.855–0.966)	0.002
Progressive hemorrhage injury		
GCS score alone	0.856 (0.774–0.917)	Reference
TP levels alone	0.801 (0.713–0.872)	NS
GCS score combined with TP	0.919 (0.850–0.963)	0.013
Posttraumatic cerebral infarction		
GCS score alone	0.816 (0.729–0.885)	Reference
TP levels alone	0.804 (0.716–0.875)	NS
GCS score combined with TP	0.898 (0.824–0.948)	0.010
6-month mortality		
GCS score alone	0.868 (0.788–0.926)	Reference
TP levels alone	0.790 (0.700–0.863)	0.145
GCS score combined with TP	0.934 (0.868–0.973)	0.005
6-month unfavorable outcome		
GCS score alone	0.886 (0.810–0.940)	Reference
TP levels alone	0.818 (0.731–0.886)	0.177
GCS score combined with TP	0.944 (0.882–0.979)	0.006

Receiver operating characteristic curves were configured as well as the results were presented as area under curve and 95% confidence interval. In a combined logistic regression model, Glasgow coma scale (GCS) score was combined with serum translocator protein (TP) levels for predicting prognosis. The additive effect of serum TP levels to GCS score was evaluated via AUC comparison by Z test.

traumatic subarachnoid hemorrhage and unreactive pupils. Taken together, TP should be a potential biomarker to assess inflammatory response after TBI.

Notably, using positron emission tomography imaging with the TP radioligand [18F] PBR111 to quantify inflammation after TBI, it was found the brain inflammation could estimate long-term functional outcome in rats with controlled cortical impact injury [35]. So, it is postulated that serum TP might be a potential biomarker for reflecting brain injury. Our study actually revealed that serum TP concentrations were strongly correlated with GCS scores utilizing partial correlation analysis for correcting other confounding factors mentioned above. However, in a recent study regarding ischemic stroke, the authors did not found a significant correlation between TP concentrations and diseases severity in a small number of patients (38 patients) [23]. Nevertheless, the present study enrolled a total of 106 patients with severe TBI. Hence, our data were more convincing. Overall, serum TP might be able to reflect extent of trauma severity after TBI.

Interestingly, a recent report has found an independent association of TP concentrations with clinical outcome and further revealed a high discriminatory ability for detecting poor prognosis in 36 patients with acute ischemic stroke [23]. However, the authors did not compare TP concentrations with clinical assessment system in terms of AUC. The current study contained ALI, ATC, PHI, PTCI, 6-month mortality and 6-month unfavorable outcome as the prognostic variables and further compared TP concentrations with GCS scores in terms of predictive ability indicated by AUC. Our intriguing findings were that serum TP emerged as an independent predictor for the aforementioned prognostic variables and showed the similar discriminatory ability for the preceding prognostic variables in terms of AUC, as compared with GCS scores. Importantly, this biomarker significantly improved the predictive value of GCS scores. In summary, determination of TP concentrations combined with GCS scores could be beneficial for accurate prognostication of TBI.

5. Conclusions

This investigation demonstrated that increased serum TP concentrations are intimately linked to the extent of inflammatory response and brain injury following head trauma and are independently related to prognosis. In conclusion, TP might be considered as a promising biomarker for reflecting brain injury and prognosis in TBI.

Acknowledgements

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