Serum TBK1 levels are correlated with inflammation, optic nerve sheath diameter and intracranial pressure in severe traumatic brain injury patients under deep sedation

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Conflict of interest
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Abstract

Background. Severe traumatic brain injuries (STBIs) cause 1/3–1/2 of trauma-related deaths. Tumor necrosis factor (TNF) receptor-associated factor NF-κB activator (TANK)-binding kinase 1 (TBK1) is a biomarker associated with inflammation, while inflammation is a key promoter of the TBI process.

Objectives. To investigate the clinical significance of TBK1 in STBI patients.

Materials and methods. The present prospective observational study included a total of 95 STBI cases diagnosed from October 2019 to October 2021. The values for optic nerve sheath diameter (ONSD) were determined under deep sedation using 2-dimensional gray scale ultrasound. Intracranial pressure (ICP) was also measured. Serum levels of TBK1 and inflammatory factors such as C-reactive protein (CRP), interleukin (IL)-1β and IL-6 were evaluated with enzyme-linked immunosorbent assay (ELISA). Clinical variables including pathological type, Glasgow Coma Scale (GCS) score, sequential organ failure assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were recorded.

Results. The levels of TBK1 in the deceased patients were remarkably lower than in the patients who survived. The IL-1β and IL-6 were markedly elevated in deceased patients compared with survivors, and negatively correlated with serum levels of TBK1. The ONSD and ICP values were significantly higher in the deceased patients than in the patients who survived and were positively correlated with each other, while both were negatively correlated with TBK1 levels. Patients with lower TBK1 expression showed significantly lower GCS scores, higher SOFA and APACHE II scores, as well as a higher 1-month mortality rate. The Kaplan–Meier curve showed that patients with higher TBK1 levels had a higher 1-month survival rate compared with the patients with lower TBK1 levels. Only TBK1 and ONSD were independent risk factors for 1-month mortality in STBI patients.

Conclusions. Lower serum TBK1 levels are associated with higher inflammatory factors, higher ONSD and ICP levels, as well as a poorer prognosis in STBI patients.

Key words: inflammation, intracranial pressure, TBK1, optic nerve sheath diameter, severe traumatic brain injury

Cite as
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Background

It has been reported that globally an estimated 96 million people suffer from traumatic brain injuries (TBIs) every year.[1] Of these TBI cases, approx. 5.48 million are severe TBIs (STBIs), which are the cause of 1/3–1/2 of trauma-related deaths.[2]

Many proteins and genes are reported to be associated with TBIs. Inflammatory factors such as C-reactive protein (CRP), tumor necrosis factor (TNF)-α and interleukin (IL)-6 are increased in TBI patients, along with the activation of the inflammatory response in TBIs.[3] The factors related to oxidative stress, such as superoxide dismutase (SOD) and inducible nitric oxide synthase (iNOS) have also been reported to be elevated in TBIs.[4–6] Additionally, neuron-specific enolase (NSE) and S100β were found to be increased in TBI patients and were correlated with the prognosis.[7,8] However, despite these findings, new potential biomarkers for the prognosis of TBIs are needed.

The TNF receptor-associated factor NF-κB activator (TANK)-binding kinase 1 (TBK1) is a well-known 82-kDa protein with 729 amino acids.[9] It has been found that TBK1 plays an important role in a variety of diseases and bioprocesses, especially inflammation and autophagy. Moreover, TBK1 inhibits inflammation and insulin resistance by phosphorylating and inducing the degradation of inhibitory-κB kinase and nuclear factor-κB (NF-κB)-inducing kinase in adipose tissue.[10] In a recent research study, it was shown that the inhibition of TBK1 resulted in an increased polymorphonuclear neutrophil necroptosis in response to lipopolysaccharide (LPS) and subsequently augmented lung inflammation.[11] The TBK1 also induces autophagy in amyotrophic lateral sclerosis, cancer and other diseases.[12–14] Since the inflammatory response is activated in TBIs and the release of cytokines is one of the main causes of brain injury, we speculated that TBK1, which is also a key factor in inflammation, might be associated with the development of TBI. However, up to now, no study has reported on the role of TBK1 in TBIs.

Objectives

In the present research, we evaluated the clinical significance of TBK1 in STBI patients and the relationship between TBK1, inflammatory factors, optic nerve sheath diameter (ONSD), and intracranial pressure (ICP), as well as the predictive value of TBK1 in the prognosis of STBI patients. This study might provide new potential biomarkers useful in the prognosis of TBIs.

Materials and methods

Patients

The present prospective observational research included a total of 95 STBI cases diagnosed from October 2019 to October 2021. All patients were enrolled after meeting the following criteria: 1) patients diagnosed with TBIs by advanced imaging including magnetic resonance imaging (MRI) and computed tomography (CT) scans; 2) STBI defined as a patient with Glasgow Coma Scale (GCS) scores from 3 to 8; 3) patients who experienced a closed craniocerebral injury; 4) patients admitted within 24 h of the trauma. The exclusion criteria included: 1) patients with open craniocerebral injuries; 2) patients with severe complications such as fractures in other body regions; 3) patients with cancer or severe renal, liver or heart diseases; 4) patients who received surgery within 3 months before the start of the study; 5) patients who were predicted to die within 24 h; 6) patients with severe ocular trauma, optic neuritis, optic nerve tumors, and other ophthalmic diseases. All patients received a routine treatment. Decompression and continuous drainage procedures were performed in all patients. No do-not-resuscitate orders were implemented for legislative reasons. This study obtained the approval from the ethics committee of the Yiyang Central Hospital, China (approval No. YY2019018). Written informed consent was obtained from all participants. The study conformed to the principles outlined in the Declaration of Helsinki.

Measurement of ONSD and ICP

Optic nerve sheath diameter and ICP were measured within 24 h of admission. The ONSD value was determined with a 2-dimensional gray scale ultrasound, using a Philips IU-22 ultrasonic diagnostic apparatus (Philips, Amsterdam, the Netherlands) with a probe frequency of 3–9 MHz. All patients were under deep sedation during the evaluation. Briefly, the probe was lightly put on the eyelid of the patient, and cross-sectional and sagittal scanning were performed twice on each side for every patient (Fig. 1). The ONSD at 3 mm behind bilateral eyeballs was recorded. For the accuracy of ONSD, it should be measured perpendicularly to the long axis of the optic nerve sheath. Every patient received 2 evaluations by 2 independent physicians. The mean value of the 2 evaluations was regarded as the ONSD value for the patient.

The intracranial pressure was measured using a Codman ICP monitor (DePuy Synthes, Raynham, USA), as reported elsewhere.[15]

Measurement of TBK1 and inflammatory factors

Blood samples of all patients were collected within 24 h of admission. Serum levels of TBK1 and inflammatory factors were determined with the enzyme-linked

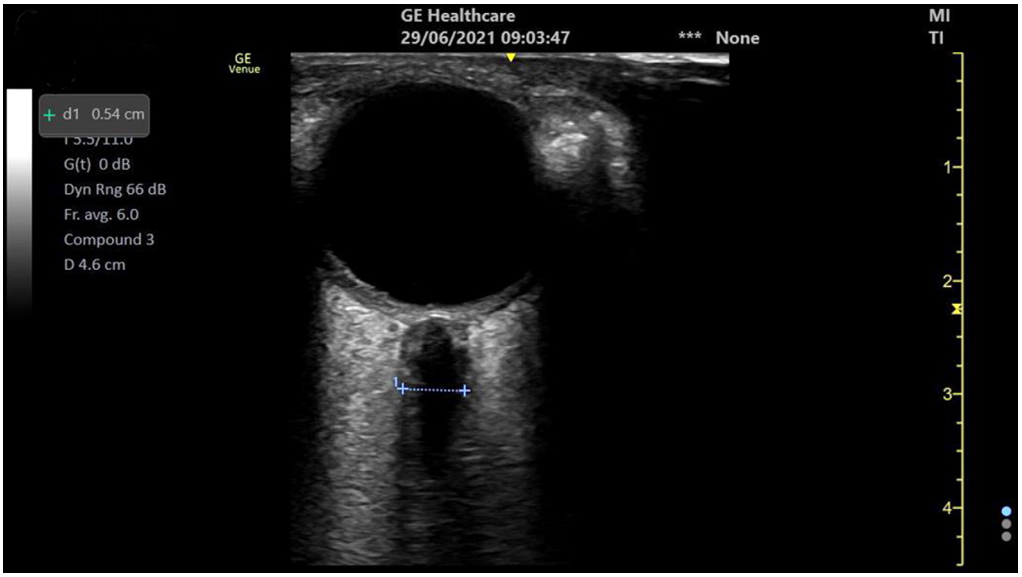

Fig. 1. Bilateral optic nerve sheath of a typical patient

immunosorbent assay (ELISA) method using the following kits according to the manufacturers' instructions: TBK1 kit (cat. No. MBS9427001; MyBioSource, San Diego, USA), CRP (cat. No. EK1316; Boster Bio, Pleasanton, USA), IL-1β (cat. No. ab214025; Abcam, Waltham, USA), and IL-6 (cat. No. ab178013; Abcam).

Data collection

Demographic data for all patients including age, sex, body mass index (BMI), and complications were collected. Clinical variables included pathological type, GCS score, sequential organ failure assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. All patients were followed up for 1 month and the 30-day mortality was analyzed. The survival duration was defined from the admission to death or the last follow-up appointment.

Statistical analyses

All normally distributed data were expressed as mean ± standard deviation (M ±SD) and non-normally distributed data were expressed as median (range). The distribution of the data was analyzed using the Kolmogorov–Smirnov test. Rates were compared using the χ^2 tests. The comparison between the 2 groups was conducted using unpaired t-tests or Mann–Whitney U tests for normally and non-normally distributed data, respectively. The Kaplan–Meier curve and log-rank test were used for survival analysis. A receiver operating characteristic (ROC) curve was used for the prediction of patient mortality by TBK1 and the cut-off value was selected using the Youden index. The Spearman's rank correlation coefficient was used to evaluate correlations due to the lack of normality of some variables. The logistic regression analysis was conducted for 1-month mortality of STBI patients using the backstepping method. The Hosmer–Lemeshow tests and Nagelkerke pseudo R^2 were used for the goodness-of-fit. All calculations were performed using SPSS v. 18.0 (SPSS Inc., Chicago, USA) and GraphPad v. 6.0 (GraphPad Software, San Diego, USA).

Results

Serum levels of TBK1 were downregulated in deceased STBI patients

The study included 95 STBI cases, of which 17 (17.89%) died within 28 days. The basic characteristics of all patients were listed in Table 1. The mean GCS ($p < 0.001$) score was markedly lower, while the SOFA ($p = 0.037$) and APACHE II scores ($p < 0.001$) were significantly higher in deceased patients compared with the survivors. No significant differences were found among the other indices.

The serum levels of TBK1 were determined. The levels of TBK1 in deceased patients were markedly lower than in the patients who survived ($p < 0.001$, Fig. 2).

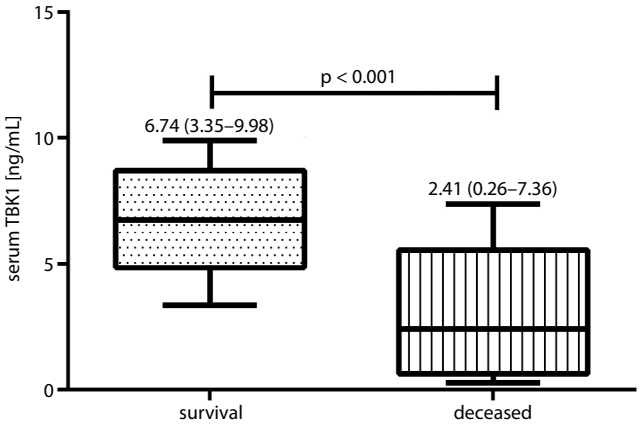

Fig. 2. Serum levels of TANK-binding kinase 1 (TBK1) in deceased and survivor severe traumatic brain injury (STBI) patients. Comparison between the 2 groups was conducted using the Mann–Whitney U test

Table 1. Basic characteristics of all STBI patients

Variables	All (n = 95)	Survival (n = 78)	Deceased (n = 17)	p-value*
Age [years]	50 (33–67)	50.5 (33–67)	49 (33–67)	0.880
Sex, male:female	62:33	51:27	11:6	0.921
BMI [kg/m^2]	23.97 (18.14–31.96)	25.13 (18.14–31.96)	22.96 (19.07–31.28)	0.088
TBI causes, n (%)				
Traffic accident	69 (72.63)	58 (74.36)	11 (64.71)	0.093
Fall	21 (22.11)	17 (21.79)	4 (23.53)	
Strike	5 (5.26)	3 (3.85)	2 (11.76)	
Pathological type, n (%)				
Intracranial hemorrhage	35 (36.84)	30 (38.46)	5 (29.41)	0.238
Severe contusion	24 (25.26)	20 (25.64)	4 (23.53)	
Subarachnoid hemorrhage	20 (21.05)	16 (20.51)	4 (23.53)	
Epidural or subdural hematoma	11 (11.58)	9 (11.54)	2 (11.76)	
Diffuse axonal injury	5 (5.26)	3 (3.85)	2 (11.76)	
Treatment strategy, n (%)				
Decompression surgery	95 (100)	78 (100)	17 (100)	1.000
Drainage treatment	95 (100)	78 (100)	17 (100)	
GCS score	6 (3–8)	7 (4–8)	5 (3–8)	<0.001
SOFA score	8.06 ±3.72	7.69 ±3.61	9.76 ±3.86	0.037
APACHE II score	16 (10–25)	15 (10–25)	21 (12–24)	<0.001

STBI – severe traumatic brain injury; BMI – body mass index; GCS – Glasgow Coma Scale; SOFA – sequential organ failure assessment; APACHE II – Acute Physiology and Chronic Health Evaluation II. * p-value was obtained by comparison between survival and deceased patients using unpaired t-test for normally distributed data or Mann–Whitney U test for non-normally distributed data or χ^2 test for rates. Normally distributed data were expressed as mean ± standard deviation (M ±SD). The non-normally distributed data were expressed as median (range). The counting data were expressed as number (rates).

Serum levels of TBK1 were correlated with serum inflammatory factors in STBI patients

To further investigate the role of TBK1 in STBI patients, the correlations between TBK1 and inflammatory factors were analyzed. It was found that IL-1β ($p < 0.001$) and IL-6 ($p = 0.028$) were elevated in deceased patients compared with survivors (Fig. 3). However, CRP showed no difference between the 2 groups. The Spearman's analysis showed that serum TBK1 levels were negatively correlated with the levels of IL-1β and IL-6, as well as SOFA and APACHE II scores. The TBK1 was positively correlated with the GCS scores (Table 2).

Table 2. Correlation between TBK1, inflammatory factors CRP, IL-1β and IL-6, as well as GCS, SOFA and APACHE II scores analyzed with Spearman's correlation analysis

Factors	Spearman's correlation	p-value
CRP	–0.148	0.152
IL-1β	–0.320	0.002
IL-6	–0.329	0.001
GCS score	0.415	<0.001
SOFA score	–0.259	0.011
APACHE II score	–0.480	<0.001

TBK1 – TANK-binding kinase 1; CRP – C-reactive protein; IL – interleukin; GCS – Glasgow Coma Scale; SOFA – sequential organ failure assessment; APACHE II – Acute Physiology and Chronic Health Evaluation II.

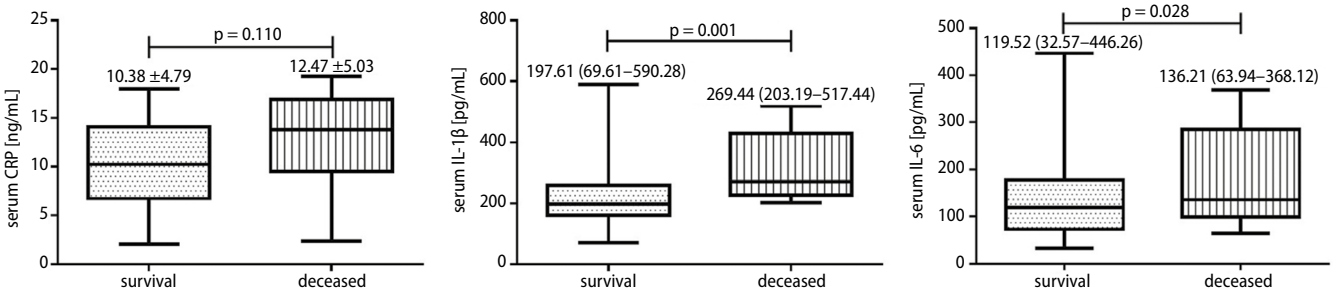

Fig. 3. Serum levels of the inflammatory factors: C-reactive protein (CRP), interleukin (IL)-1β and IL-6 in deceased and survivor severe traumatic brain injury (STBI) patients. Comparison between the 2 groups was conducted using the unpaired t-test or Mann–Whitney U test for normally and non-normally distributed data, respectively

Serum levels of TBK1 were correlated with levels of ONSD and ICP in STBI patients

Next, ONSD and ICP values were analyzed. As shown in Fig. 4A, the values of ONSD ($p < 0.001$) and ICP ($p = 0.001$) were significantly increased in the deceased patients compared to the patients who survived. Additionally, the ONSD values were positively correlated with ICP values using the Spearman's analysis ($p = 0.012$; Fig. 4B). We divided all patients into TBK1 high expression and low expression groups according to the mean value of TBK1 (6.10 ng/mL). The GCS scores were used as a hierarchical variable during comparison. It was found that patients with lower TBK1 levels showed higher ONSD and ICP levels ($p = 0.024$ and $p = 0.006$, respectively; Table 3). The Spearman's analysis found that serum levels of TBK1 were negatively correlated with ONSD (Spearman's correlation: −0.206, $p = 0.044$) and ICP (Spearman's correlation: −0.294, $p < 0.004$). These results indicated that serum TBK1 levels and ONSD could predict the alteration in ICPs in STBI patients.

Table 3. ONSD and ICP in STBI patients with different expression of TBK1

Variables	High TBK1 (n = 50)	Low TBK1 (n = 45)	p-value*
ONSD [mm]	4.20 ±0.40	4.40 ±0.48	0.024
ICP [mm H_2O]	178.77 ±57.91	216.78 ±73.82	0.006

ONSD – optic nerve sheath diameter; ICP – intracranial pressure; STBI – severe traumatic brain injury; TBK1 – TANK-binding kinase 1.
* Comparison was made using the unpaired t-test for normally distributed data between the 2 groups.

Relationship between TBK1 and clinical outcomes and prognosis in STBI patients

We analyzed the clinical outcomes in STBI patients with different expression levels of TBK1. The GCS scores were used as a hierarchical variable when comparing continuous data using a t-test. It was found that patients with lower TBK1 expression showed significantly lower GCS scores ($p < 0.001$), higher SOFA ($p = 0.014$) and APACHE II ($p < 0.001$) scores, as well as higher 1-month mortality ($p < 0.001$; Table 4). Furthermore, the Kaplan–Meier curve showed that the patients with higher TBK1 levels had a longer 1-month survival compared to the patients with lower TBK1 levels ($p = 0.007$; Fig. 5A). The ROC curve showed that TBK1 has the potential to predict 1-month mortality of STBI patients using a cutoff value <4.59 ng/mL with an area under the curve (AUC) = 0.850, a sensitivity of 76.47%, and a specificity of 78.12%. Additionally, the logistic regression analysis was conducted to identify factors that showed significant differences in univariate analysis. The Hosmer–Lemeshow tests showed that the goodness-of-fit ($p = 0.633$) and the Nagelkerke pseudo R^2 values were 0.443 and 0.557, respectively, indicating that the goodness-of-fit was acceptable. It was found that only TBK1 and ONSD were independent risk factors for 1-month mortality in STBI patients ($p < 0.001$ and $p = 0.014$, respectively; Table 5).

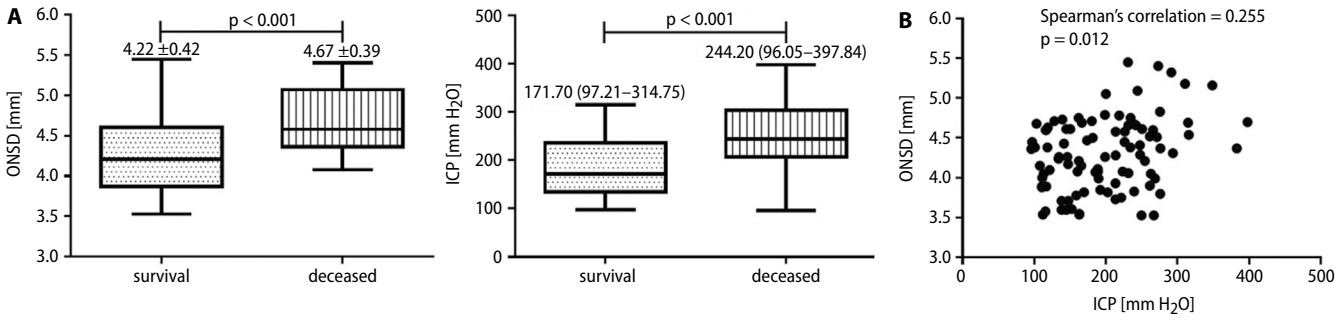

Fig. 4. A. Optic nerve sheath diameter (ONSD) and intracranial pressure (ICP) in deceased and survivor severe traumatic brain injury (STBI) patients. Comparison between the 2 groups was conducted using the unpaired t-test or Mann–Whitney U test for normally and non-normally distributed data, respectively; B. Correlation between ONSD and ICP in all STBI patients calculated using the Spearman's correlation

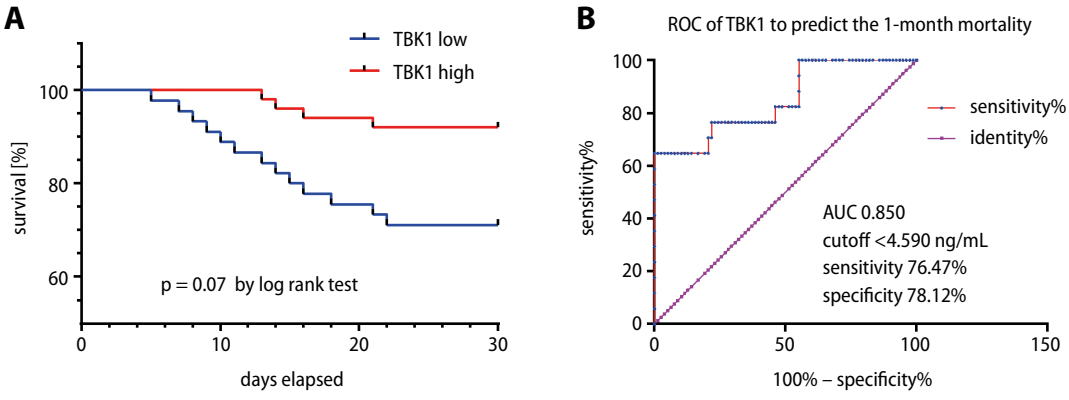

Fig. 5. A. The Kaplan–Meier curve for patients with different expression levels of TANK-binding kinase 1 (TBK1); B. Receiver operating characteristic (ROC) curve was used to predict the 1-month mortality using TBK1

AUC – area under the curve.

Table 4. Relationship between TBK1 and clinical outcomes and prognosis of STBI patients

Variables	High TBK1 (n = 50)	Low TBK1 (n = 45)	p-value*
Age [years]	49.00 ±10.75	49.75 ±10.34	0.729
Male:female	35:15	27:18	0.138
BMI [kg/m^2]	23.55 (18.14–31.96)	24.76 (18.79–31.90)	0.744
TBI causes, n (%)			
Traffic accident	36 (72.00)	33 (73.33)	0.593
Fall	12 (24.00)	9 (20.00)	
Strike	2 (4.00)	3 (6.67)	
Pathological type, n (%)			
Intracranial hemorrhage	20 (40.00)	15 (33.33)	0.494
Severe contusion	14 (28.00)	10 (22.22)	
Subarachnoid hemorrhage	9 (18.00)	11 (24.44)	
Epidural or subdural hematoma	5 (10.00)	6 (13.33)	
Diffuse axonal injury	2 (4.00)	3 (6.67)	
GCS score	5 (3–8)	7 (5–8)	<0.001
SOFA score	7.18 ±3.76	9.04 ±3.46	0.014
APACHE II score	20 (10–25)	15 (10–21)	<0.001
1-month mortality, n (%)	4 (8.00)	12 (26.67)	<0.001

TBK1 – TANK-binding kinase 1; STBI – severe traumatic brain injury; BMI – body mass index; GCS – Glasgow Coma Scale; SOFA – sequential organ failure assessment; APACHE II – Acute Physiology and Chronic Health Evaluation II. * p-value was obtained by comparison between survival and deceased patients using the unpaired t-test for normally distributed data or Mann–Whitney U test for non-normally distributed data χ^2 test for rates. The normally distributed data were expressed as mean ± standard deviation (M ±SD). The non-normally distributed data were expressed as median (range). The counting data were expressed as number (rates).

Table 5. Logistic regression for risk factors of 1-month mortality in STBI patients

Variables	Wald	OR	95% CI	p-value
GCS score	1.422	0.675	0.354–1.288	0.233
SOFA score	0.101	0.952	0.702–1.291	0.750
APACHE II score	0.635	1.120	0.848–1.479	0.426
TBK1	13.241	0.507	0.352–0.731	<0.001
CRP	0.945	0.913	0.759–1.097	0.331
IL-1β	1.614	1.004	0.998–1.011	0.204
IL-6	2.232	0.992	0.982–1.002	0.135
ONSD	6.018	8.837	1.550–50.395	0.014
ICP	0.674	1.006	0.992–1.019	0.412

STBI – severe traumatic brain injury; GCS – Glasgow Coma Scale; SOFA – sequential organ failure assessment; APACHE II – Acute Physiology and Chronic Health Evaluation II; TBK1 – TANK-binding kinase 1; CRP – C-reactive protein; IL – interleukin; ONSD – optic nerve sheath diameter; ICP – intracranial pressure; OR – odds ratio; 95% CI – 95% confidence interval.

Discussion

There are many factors influencing the prognosis of TBI patients. However, new factors associated with TBI are still needed. In the present study, we demonstrated that serum TBK1 levels were decreased in STBI patients and were correlated with increased inflammation, ONSD, ICP, as well as a poor prognosis.

The TBK1 is a protein that plays an important role in many diseases, inflammation and organ injuries. In TBK1-knockdown mice, the decreased expression of TBK1 significantly increased neuroinflammation by the activation of receptor-interacting protein kinase 1 (RIPK1) activity in aging human and animal models, while an increased expression of TBK1 inhibited neuroinflammation.[16] In high-fat diet (HFD)-induced obesity, a deficiency in TBK1 facilitated the inflammation through the regulation of AMP-activated protein kinase (AMPK) signaling, while the overexpression of TBK1 suppressed the inflammation by attenuating NF-κB activity in adipose tissue.[10] In pancreatic inflammation, the inhibition of TBK1 inhibited autophagy and upregulated the inflammatory response.[17] In TBK1-deficient mice, an increased susceptibility to LPS-induced lethality and immune cell

infiltrates in multiple tissues were observed.[18] Additionally, TBK1 and IL-1β were reported to induce autophagy in macrophages, and TBK1 was essential for IL-1β-induced autophagy, indicating the relationship between TBK1, autophagy and inflammation.[19] All these studies indicated that TBK1 plays a key role in inflammation and can suppress the inflammation in bioprocesses, including neuroinflammation. In this study, we found that serum TBK1 levels were negatively correlated with serum levels of inflammatory factors. Increased inflammatory factors were found in TBI patients in many studies.[20–22] Generally, the inflammatory process is activated during TBIs, which may in turn accelerate brain injury.[23] We also found that lower TBK1 levels predicted a poor prognosis for STBI patients, indicating that TBK1 can influence the progression of TBIs, which might be associated with the inflammatory response.

The relationship between ONSD and ICP has been noticed in several studies, including studies on TBIs. Legrand et al. demonstrated that the mean ONSD value was significantly higher (7.8 ±0.1 mm) in the deceased TBI patients compared to survivors (6.8 ±0.1 mm), and lower values of ONSD predicted a better 6-month survival.[24] In another study, Sekhon et al. found that each 1-millimeter increase in ONSD was associated with a twofold increase in hospital mortality in TBI patients, while ONSD was independently associated with increased ICPs within 48 h of admission.[25] Young et al. observed that ONSD was positively correlated with ICPs, and pediatric patients with an ONSD > 6.1 mm needed careful ICP monitoring.[26] In our research, we also observed that ONSD and ICP levels were elevated and positively correlated in the deceased STBI patients, which is consistent with the abovementioned findings. Interestingly, serum levels of TBK1 were negatively correlated with the values of ONSD and ICP. However, the meaning of this phenomenon requires more studies to confirm.

Limitations

The present study has several limitations. First, we only included a small sample of the study population. Secondly, only a few inflammatory factors were detected and more inflammatory factors could have been tested. Thirdly, we did not test the levels of TBK1 in cerebrospinal fluid. Finally, we excluded patients who were expected to die within 24 h of admission, which might have introduced bias into our study.

Conclusions

This study demonstrated that lower serum TBK1 levels were associated with increased inflammation, higher ONSD and ICP levels, as well as a poorer prognosis in STBI patients. The presented research provides more clinical evidence for TBK1 in TBIs.

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References

1. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg*. 2019;130(4):1080–1097. doi:10.3171/2017.10.JNS17352
2. Faul M, Coronado V. Epidemiology of traumatic brain injury. In: *Handbook of Clinical Neurology*. Vol 127. Amsterdam, the Netherlands: Elsevier; 2015:3–13. doi:10.1016/B978-0-444-52892-6.00001-5
3. Yang DB, Yu WH, Dong XQ, et al. Serum macrophage migration inhibitory factor concentrations correlate with prognosis of traumatic brain injury. *Clinica Chim Acta*. 2017;469:99–104. doi:10.1016/j.cca.2017.03.030
4. Liao Y, Liu P, Guo F, Zhang ZY, Zhang Z. Oxidative burst of circulating neutrophils following traumatic brain injury in human. *PLoS One*. 2013;8(7):e68963. doi:10.1371/journal.pone.0068963
5. Wei LF, Zhang HM, Wabg SS, et al. Changes of MDA and SOD in brain tissue after secondary brain injury with seawater immersion in rats. *Turk Neurosurg*. 2013;26(3):384–388. doi:10.5137/1019-5149.JTN.8265-13.1
6. Hall ED, Wang JA, Miller DM, Cebak JE, Hill RL. Newer pharmacological approaches for antioxidant neuroprotection in traumatic brain injury. *Neuropharmacology*. 2019;145:247–258. doi:10.1016/j.neuropharm.2018.08.005
7. Agoston DV, Shutes-David A, Peskind ER. Biofluid biomarkers of traumatic brain injury. *Brain Inj*. 2017;31(9):1195–1203. doi:10.1080/02699052.2017.1357836
8. Papa L, Silvestri S, Brophy GM, et al. GFAP outperforms S100β in detecting traumatic intracranial lesions on computed tomography in trauma patients with mild traumatic brain injury and those with extracranial lesions. *J Neurotrauma*. 2014;31(22):1815–1822. doi:10.1089/neu.2013.3245
9. Ahmad L, Zhang SY, Casanova JL, Sancho-Shimizu V. Human TBK1: A gatekeeper of neuroinflammation. *Trends Mol Med*. 2016;22(6):511–527. doi:10.1016/j.molmed.2016.04.006
10. Zhao P, Wong KI, Sun X, et al. TBK1 at the crossroads of inflammation and energy homeostasis in adipose tissue. *Cell*. 2018;172(4):731.e12–743.e12. doi:10.1016/j.cell.2018.01.007
11. Wang J, Luan Y, Fan EK, et al. TBK1/IKKε negatively regulate LPS-induced neutrophil necroptosis and lung inflammation. *Shock*. 2021;55(3):338–348. doi:10.1097/SHK.0000000000001632
12. Newman AC, Scholefield CL, Kemp AJ, et al. TBK1 kinase addiction in lung cancer cells is mediated via autophagy of Tax1bp1/Ndp52 and non-canonical NF-κB signalling. *PLoS One*. 2012;7(11):e50672. doi:10.1371/journal.pone.0050672
13. Oakes JA, Davies MC, Collins MO. TBK1: A new player in ALS linking autophagy and neuroinflammation. *Mol Brain*. 2017;10(1):5. doi:10.1186/s13041-017-0287-x
14. Richter B, Sliter DA, Herhaus L, et al. Phosphorylation of OPTN by TBK1 enhances its binding to Ub chains and promotes selective autophagy of damaged mitochondria. *Proc Natl Acad Sci U S A*. 2016;113(15):4039–4044. doi:10.1073/pnas.1523926113
15. Lescot T, Reina V, Le Manach Y, et al. In vivo accuracy of two intraparenchymal intracranial pressure monitors. *Intensive Care Med*. 2011;37(5):875–879. doi:10.1007/s00134-011-2182-8
16. Xu D, Jin T, Zhu H, et al. TBK1 suppresses RIPK1-driven apoptosis and inflammation during development and in aging. *Cell*. 2018;174(6):1477.e19–1491.e19. doi:10.1016/j.cell.2018.07.041
17. Yang S, Imamura Y, Jenkins RW, et al. Autophagy inhibition dysregulates TBK1 signaling and promotes pancreatic inflammation. *Cancer Immun Res*. 2016;4(6):520–530. doi:10.1158/2326-6066.CIR-15-0235
18. Marchlik E, Thakker P, Carlson T, et al. Mice lacking Tbk1 activity exhibit immune cell infiltrates in multiple tissues and increased susceptibility to LPS-induced lethality. *J Leukoc Biol*. 2010;88(6):1171–1180. doi:10.1189/jlb.0210071

19. Pilli M, Arko-Mensah J, Ponpuak M, et al. TBK-1 promotes autophagy-mediated antimicrobial defense by controlling autophagosome maturation. *Immunity*. 2012;37(2):223–234. doi:10.1016/j.immuni.2012.04.015
20. Ramlackhansingh AF, Brooks DJ, Greenwood RJ, et al. Inflammation after trauma: Microglial activation and traumatic brain injury. *Ann Neurol*. 2011;70(3):374–383. doi:10.1002/ana.22455
21. Ziebell JM, Morganti-Kossmann MC. Involvement of pro- and anti-inflammatory cytokines and chemokines in the pathophysiology of traumatic brain injury. *Neurotherapeutics*. 2010;7(1):22–30. doi:10.1016/j.nurt.2009.10.016
22. Webster KM, Sun M, Crack P, O'Brien TJ, Shultz SR, Semple BD. Inflammation in epileptogenesis after traumatic brain injury. *J Neuroinflammation*. 2017;14(1):10. doi:10.1186/s12974-016-0786-1
23. Shi K, Zhang J, Dong JF, Shi FD. Dissemination of brain inflammation in traumatic brain injury. *Cell Mol Immunol*. 2019;16(6):523–530. doi:10.1038/s41423-019-0213-5
24. Legrand A, Jeanjean P, Delanghe F, Peltier J, Lecat B, Dupont H. Estimation of optic nerve sheath diameter on an initial brain computed tomography scan can contribute prognostic information in traumatic brain injury patients. *Crit Care*. 2013;17(2):R61. doi:10.1186/cc12589
25. Sekhon MS, McBeth P, Zou J, et al. Association between optic nerve sheath diameter and mortality in patients with severe traumatic brain injury. *Neurocrit Care*. 2014;21(2):245–252. doi:10.1007/s12028-014-0003-y
26. Young AMH, Guilfoyle MR, Donnelly J, et al. Correlating optic nerve sheath diameter with opening intracranial pressure in pediatric traumatic brain injury. *Pediatr Res*. 2017;81(3):443–447. doi:10.1038/pr.2016.165