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Prognostic Significance of Translocator Protein in Brain Tissue Following Traumatic Brain Injury

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ABSTRACT

AIM: To measure the expression of translocator protein (TSPO) in brain tissue following traumatic brain injury (TBI) and determine whether TSPO can predict patient outcomes.

MATERIAL and METHODS: TBI patients requiring removal of intracranial hematoma were recruited from Wujin Hospital Affiliated with Jiangsu University between January 2018 and March 2021. TBI patients were divided into unfavorable and favorable groups according to the Glasgow Outcome Scale (GOS) score. The level of TSPO in brain samples was analyzed by Western blot and immunocytochemistry.

RESULTS: The expression of TSPO in the unfavorable group was higher than that in the favorable group. Double immunofluorescence staining showed that the percentages of TSPO positive cells among IBA1 positive and GFAP positive cells were 45.2± 3.1% and 3.5±0.6% respectively. After adjusting for age, sex, Computed tomography (CT), intracranial pressure (ICP) and Glasgow coma scale (GCS), we found that each 1-unit increase in TSPO was associated with a 40% higher occurrence of an unfavorable outcome (OR =1.4, 95% CI 0.4-5.6). The area under the receiver operating characteristic curve (AUC), specificity, and sensitivity of TSPO were 0.87, 76.7%, 88.2% respectively.

CONCLUSION: Our study demonstrated that higher TSPO expression was associated with a higher occurrence of unfavorable outcomes.

KEYWORDS: TBI, Translocator protein, Multivariate logistic regression, Receiver operating characteristic curve

INTRODUCTION

Traumatic brain injury (TBI) remains the primary reason for mortality in persons younger than 45 years worldwide (7,10,28). Consequently, many studies have focused on the mechanism underlying TBI. Previous studies have shown that oxidative stress, the neuroinflammatory response, apoptosis, and inflammatory activities may play important roles in the secondary injury of TBI. Several biomarkers including inflammatory and apoptosis factors in blood samples and cerebrospinal fluid (CSF) were proven to be associated with mortality in TBI patients (5,10,11,13,14). As research on the mechanisms underlying TBI advance, more novel and reliable markers for predicting the outcome of TBI have been identified.

The expression of the 18-kDa translocator protein (TSPO) is very low in the brain and restricted to glial cells under normal physiological conditions. Previous studies have demonstrated that TSPO expression was linked with brain injury, neuroinflammation and neurodegenerative diseases (3,22). Donat et al. found the increase of TSPO mRNA at the contusion site of TBI rate model using radioligand binding method (6). Multiple researchers have applied TSPO as a

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marker of brain injury using positron emission tomography (PET) in experimental animals and humans (20,23,26). Recently, it was reported that serum TSPO was associated with the outcome of patients with traumatic brain injury and acute ischemic stroke, and the use of TSPO-specific ligands may have therapeutic implications in brain injury (3,15).

However, few studies have focused on the expression of TSPO in TBI patient brain tissue. The aim of this study was to measure the expression of TSPO in TBI patient brain tissue using Western blot and immunofluorescence and to explore whether TSPO can predict patient outcomes in TBI.

MATERIAL and METHODS

Subject

Patients with TBI were recruited at the Department of Neurosurgery, Wujin Hospital Affiliated with Jiangsu University between January 2018 and March 2021. A diagnosis of TBI required a clear history of injuries and a positive cranial CT scan including acute subdural hematoma (aSDH), mixed density SDH (mSDH), extradural hematoma (EDH), intraventricular hemorrhage (IVH) and intraparenchymal hemorrhage (IPH) according to the Common Data Element (CDE) scheme for TBI (https://commondataelements.ninds.nih.gov/) (8,27,32). The patients received medical treatment according to the Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition (Neurosurgery. 2016 Sep 20) (2). Patients first underwent implantation of an intraparenchymal ICP monitor in the operation room before any further surgical intervention. For all TBI subjects, the inclusion criteria were as follows: 1) patient age between 16 and 70 years, 2) emergency removal of intracranial hematoma and brain tissues, 3) no current or history of neurologic disease, or bleeding disorder, and 4) signed consent from next-of-kin.

Ultimately, 91 patients with TBI were included. This clinical study followed the Declaration of Helsinki, and was approved by the Medical Ethics Committee of Wujin Hospital Affiliated with Jiangsu University (NO. 2018-07). A written informed consent was obtained from each participant or their relations.

Demographic and Clinical Injury Variables

Independent variables included sex, age, body mass index (BMI), diabetes, hypertension, hyperlipidemia, systolic blood pressure (SBP), diastolic blood pressure (DBP), initial GCS (Glasgow coma scale), ICP (intracranial pressure). time to the operating room and Helsinki CT score. The duration from trauma occurrence to surgery was calculated and defined as the time to the operating room. The GCS was taken within 8 hours of injury to limit the influence of alcohol, sedatives, or paralytics. The level of brain injury was determined according to the Helsinki score on initial CT findings.

Outcome Variables

The Glasgow outcome score (GOS) of the subjects were assessed 6 months after injury. Patients were assigned to the good recovery (5), moderate disability (4), severe disability (3), persistent vegetative state (2), or death (1). For this study, all TBI patients were divided into an unfavorable outcome group (1/2/3) and a favorable outcome group (4/5).

Samples

Brain samples were obtained from surgically resected areas of contusions in TBI patients requiring emergency craniotomy for mass effects in our hospital. All brain samples were stored in liquid nitrogen.

Western Blot

The expression of TSPO in brain samples was measured using the Western blot. Samples (20μg) were homogenized in chilled lysis buffer and centrifuged at 4500 × g for 20 minutes. The supernatant was collected to analyze proteins using the Bio-Rad protein assay (Bio-Rad, California, USA). Using a wet electroblotting system, we transferred the separated proteins to PVDF membranes (Millipore Corporation, Billerica, MA, USA) for 2 hours, and then blocked them in TBST (50 mM Tris–HCl, 0.1% Tween 20, 154 mM NaCl, pH = 7.3) for 2 hours. Primary antibodies (rabbit anti-PBR, 1:1000, ab109497, Abcam) were used to incubate samples overnight in TBST. Secondary antibodies (goat anti-rabbit coupled to horseradish peroxidase, Jackson ImmunoResearch, West Grove, PA, 1:3000 dilution) were used to incubate the PVDF membranes for 2 hours at room temperature. The immunoreactive bands were visualized by an ECL kit (Thermo, USA). β-actin was used to normalize all cytosolic protein bands. Immunoblots were scanned by a densitometer and the gray value was analyzed by Quantity One software (BioRad, USA) (12).

Immunocytochemistry

The samples were soaked in 4% paraformaldehyde and 30% sucrose for 24 hours. The samples were frozen and 10 μm thick serial coronal sections were made using a cryostat. Tissue sections were placed in phosphate buffered saline (0.01 M PBS) for 30 minutes, blocked with 5% normal goat serum, and then placed in 0.2% Triton X-100 for 90 minutes. Rabbit anti-PBR (ab109497, Abcam) at 1:100 was used to incubate the sections over two nights at 4 °C. After the primary antibody incubation, the tissue sections were washed three times in 0.01 M PBS. Double immunostaining was performed by incubating with a mixture of anti-PBR and goat anti-IBA1 polyclonal antibody (Abcam, ab107159, 1:100, microglial cell) or rabbit anti-GFAP polyclonal antibody (Sigma, G9269, 1:1000, astrocyte) overnight at 4 °C. All the above sections were treated with a mixture of FITC- and Cy3-conjugated secondary antibodies (1:300, Jackson ImmunoResearch, USA) for 1 hour at room temperature. The sections were rinsed in 0.01 M PBS three times, mounted on a gelatin-coated slide and dried in air. 2.5 x 2.5 mm segments of tissue extending were captured at 20X objective power by a fluorescence microscope attached to a CCD spot camera (LEICA DFC350FX/DMIRB, Germany). Then, the images were processed with LEICA IM50 software (Germany) (12). Quantification of the immunofluorescence staining was performed by counting the number of TSPO immunoreactivity (IR) positive cells per section. For each patient every fourth section was picked from a series of consecutive brain tissue sections (10 μm), and four to six sections were counted for

each patient. The total number of TSPO-IR positive cells was divided by the total number of toluidine blue stained profiles in brain tissue sections, and the percentage of immunoreactive cells was calculated.

Quantification and Statistical Analysis

Measurement data are expressed as the mean ± SD, and enumeration data are expressed as percentages. Differences between the groups were statistically analyzed using the t-test, Wilcoxon tests or the $\chi 2$ test depending on the type of variable. Partial correlation analysis between TSPO expression and ICP, GOS, Helsinki score and time to operating room was performed. Univariate analysis was used to determine the significance of the association between TSPO expression and the outcome. Multivariate logistic regression was employed to determine the independent association between TSPO expression and the outcome following TBI. The results are shown as odds ratios (ORs), 95% confidence intervals (95% CIs) and p values. To evaluate the reliability and the net benefit of the nomogram, we applied receiver operating characteristic (ROC) curve analysis and plotted, calibration curves and decision curves. SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analyses. A p value less than 0.05 was regarded as statistically significant.

RESULTS

Clinical Characteristics of Patients with TBI

Ultimately, 91 TBI patients were recruited into our study. According to the outcomes of the patients, 65 and 26 patients were included in the favorable and unfavorable outcome groups respectively. There was no significant difference between the two groups in age, sex, BMI (body mass index), diabetes, hypertension, hyperlipidemia, SBP, DBP or initial GCS ($p>0.05$). However, the ICP, Helsinki CT score, and time to the operating room were higher in the unfavorable outcome group than that in the favorable outcome group ($p<0.05$) (Table I).

Expression of TSPO

Western blot analysis showed that the relative TSPO protein expression in the unfavorable outcome group was 0.85 ± 0.09, which was higher than that in the favorable outcome group (0.32 ± 0.04) ($p<0.05$). Immunocytochemistry showed that the percentage of TSPO positive cells in unfavorable outcome group was 40.3 ± 9.1%, which was higher than that in the favorable outcome group (12.9 ± 4.8%) ($p<0.05$) (Table I, Figure 1A-D). Double immunofluorescence staining showed that TSPO colocalized with IBA1 and GFAP. Moreover, the percentages of TSPO positive in IBA1 and GFAP positive cells were 46.3 ± 3.5% and 3.1 ± 0.7% respectively, which meant that TSPO was expressed mainly in microglia (Figure 2A-F).

Table I: Clinical Summary of Patients' Data

Items	Favorable outcome group (N=65)	Unfavorable outcome group (N=26)	p
Age (year)	31.64 ± 13.63	30.81 ± 9.88	0.778
Sex			0.352
Male	37 (56.9%)	12 (46.2%)	
Female	28 (43.1%)	14 (53.8%)	
Body mass index (kg/m^2)	26.07 ± 3.46	25.21 ± 2.44	0.227
Diabetes (n, %)	14 (21.5%)	8 (30.8%)	0.353
Hypertension (n, %)	34 (52.3%)	15 (57.7%)	0.642
Hyperlipidemia (n, %)	6 (9.2%)	4 (15.4%)	0.396
SBP (mmHg)	146.62 ± 22.98	157.69 ± 26.01	0.065
DBP (mmHg)	88.97 ± 14.98	85.50 ± 15.71	0.328
Helsinki CT score	6.32 ± 1.91	9.35 ± 2.08	<0.001
ICP (mmHg)	19.45 ± 6.84	28.08 ± 6.17	<0.001
TSPO (ratio)	0.32 ± 0.04	0.85 ± 0.09	<0.001
Time to operating room (h)	2.09 ± 1.55	3.05 ± 0.88	0.004
GCS			0.256
<=8	54 (83.1%)	24 (92.3%)	
>8	11 (16.9%)	2 (7.7%)	

ICP: *Intracranial pressure,* ***TSPO:*** *Translocator protein,* ***GCS:*** *Glasgow Coma Score,* ***SBP:*** *Systolic blood pressure,* ***DBP:*** *Diastolic blood pressure*

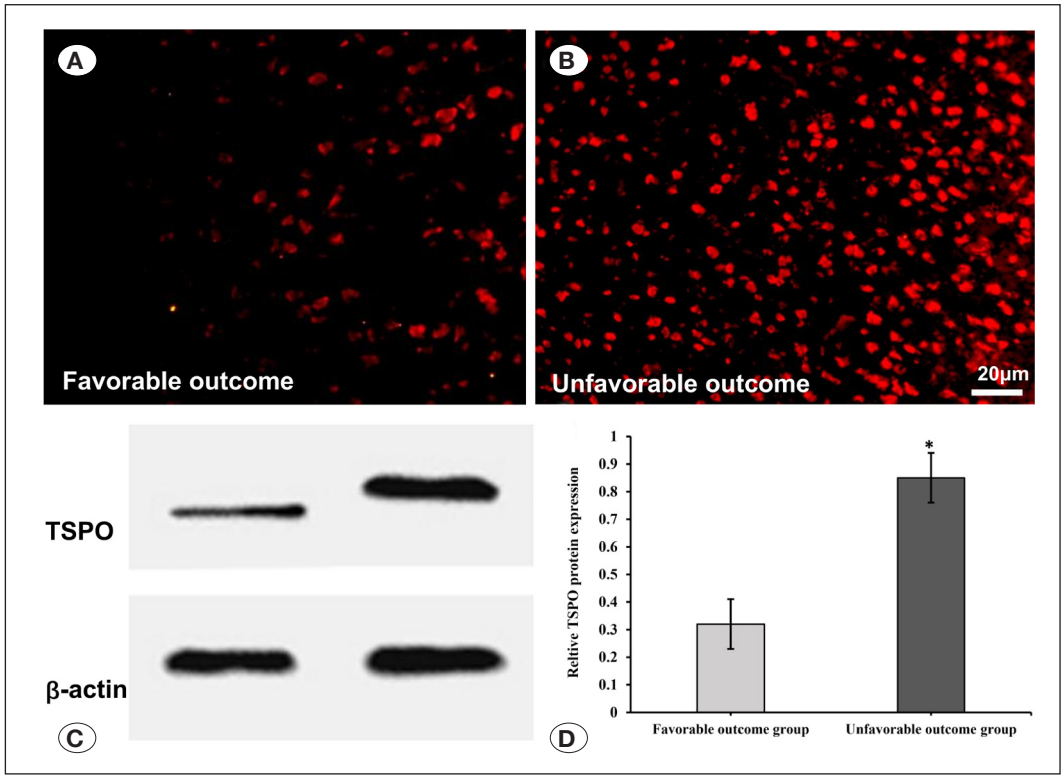

Figure 1: The expression of TSPO in the brain tissue. The western blot showed that the relative TSPO protein in the unfavorable outcome group was 1.29 ± 0.29, which was higher than that in the favorable outcome group (0.81 ± 0.27) **(C, D)**. The immunocytochemistry showed that the percentage of TSPO positive cells in unfavorable outcome group was 40.3 ± 9.1% **(B)**, which was higher than that in the favorable outcome group (12.9 ± 4.8) **(A)**. *p<0.05 versus favorable outcome group.

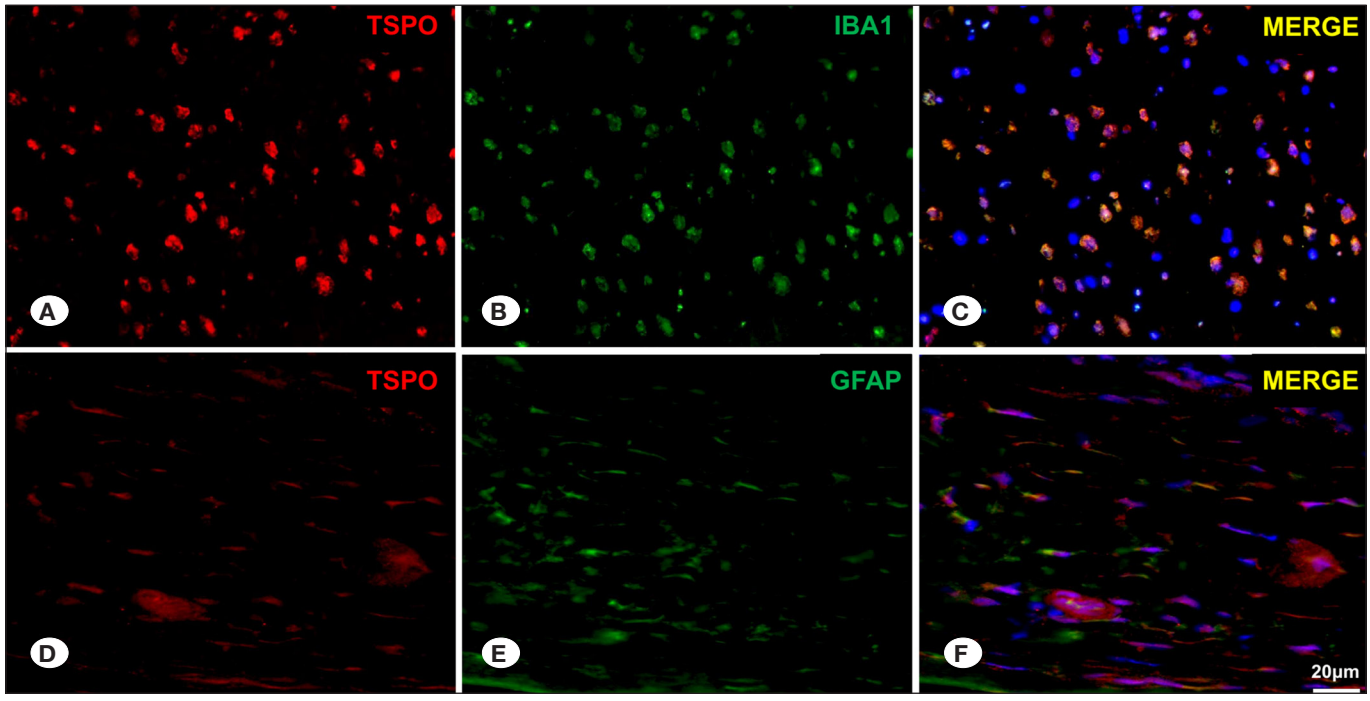

Figure 2: Double immunofluorescence staining in the brain tissue. Double immunofluorescence staining exhibited that TSPO co-localized with IBA1 **(A-C)** and GFAP **(D-F)**. Moreover, the percentage of TSPO positive cells in IBA1 and GFAP positive cells was 45.2± 3.1% and 3.5±0.6% respectively, which meant the TSPO expressed mainly in microglia.

Relationship Between TSPO and Other Variables

Partial correlation analysis was performed between TSPO expression and ICP, GOS, Helsinki CT score and time to operating room. The level of TSPO was significantly correlated with ICP (R^2=0.387, p<0.01) and time to the operating room (R^2=0.494, p<0.01) but not with the GOS or Helsinki CT score (p>0.05) (Figure 3A-D).

Relationship Between TSPO Expression and Outcome

Univariate regression analysis was performed to determine the relationships between clinical parameters and outcome. As shown in Table II, we observed a significant correlation between the Helsinki CT score, ICP, TSPO expression, time to operating room and the outcome following TBI (p<0.05). The odds ratio (OR) of TSPO expression for outcome was 4.848, which meant that a higher TSPO level led to an increase in the rate of an unfavorable outcome (Table II).

Multivariate logistic regression was employed to determine the independent association between TSPO and the outcome of TBI. We also analyzed the influence of covariates on outcome. Table III and IV show the associations of each confounder with outcome. We selected confounders based on their associations with outcomes for an effect estimate of more than 10%. Consequently, we adjusted the covariates including ICP, time to operating room, Helsinki CT score, body mass index, SBP, and hyperlipidemia in the logistic regression model. In model I (adjusting for age and sex), we found that each 1-unit increase in TSPO expression was associated with a 4.5-fold higher occurrence of unfavorable outcomes after adjusting for age and sex (OR =5.5, 95% CI 2.7-10.9; p<0.001). We also converted TSPO expression from a continuous variable to a binary categorical variable depending on the mean level of TSPO. Compared to a TSPO level <0.95, a TSPO level >=0.95 was associated with a higher occurrence of unfavorable outcomes (OR=13.1, 95% CI 3.5-48.5, p<0.001). In the

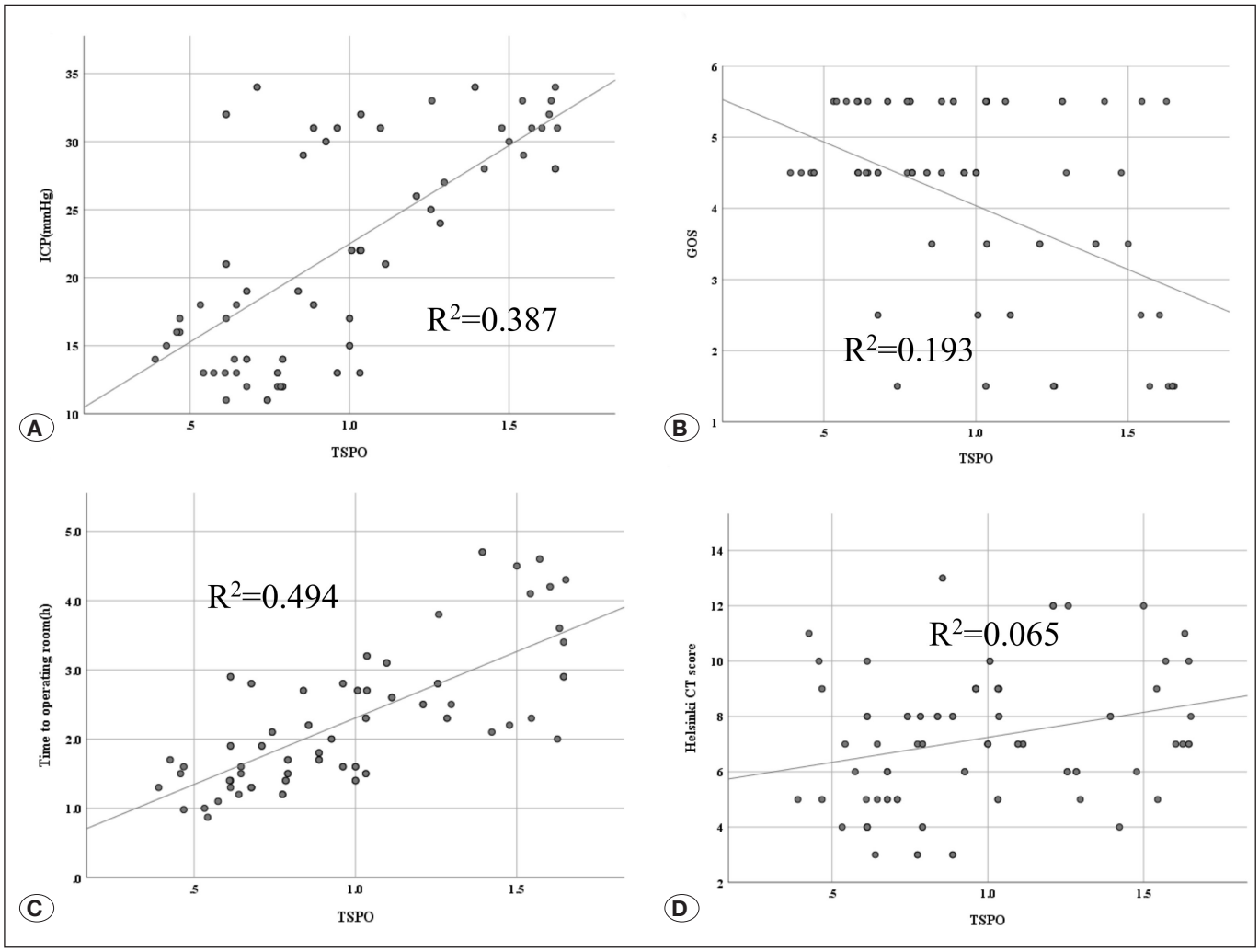

Figure 3: Relationship between TSPO and other variables. The level of TSPO was significantly correlated with the ICP (R^2=0.387, p< 0.01) **(A)** and time to operating room (R^2= 0.494, p<0.01) **(C)**. While the TSPO was not significantly correlated with GOS **(B)** or Helsinki CT score (p>0.05) **(D)**.

Table II: Univariate Analysis for Outcome

Items	OR (95%CI)	p
Age (year)	0.995 (0.959, 1.032)	0.775
Sex		
Male	Reference	
Female	0.649 (0.260, 1.618)	0.353
Body mass index(kg/m²)	0.916 (0.789, 1.063)	0.248
Diabetes (Yes)	0.618 (0.222, 1.715)	0.355
Hypertension (Yes)	0.804 (0.321, 2.014)	0.642
Hyperlipidemia (Yes)	0.559 (0.144, 2.172)	0.401
SBP (mmHg)	1.019 (1.000, 1.039)	0.053
DBP (mmHg)	0.985 (0.955, 1.015)	0.324
Helsinki CT score	2.168 (1.529, 3.074)	<0.001
ICP (mmHg)	1.198 (1.103, 1.301)	<0.001
TSPO (ratio)	4.848 (2.547, 9.228)	<0.001
Time to operating room(h)	1.911 (1.150, 3.176)	0.012
GCS		
<=8	Reference	
>8	0.409 (0.084, 1.989)	0.268

CI: *Confidence interval,* ***OR:*** *Odds ratio.*

fully adjusted model (model II, adjusting for ICP, time to the operating room, Helsinki CT score, body mass index, SBP, hyperlipidemia), we found that each 1-unit increase in TSPO was associated with an 11.0-fold occurrence of unfavorable outcomes (OR=12.0, 95% CI 1.5-93.2, p=0.018). Compared to a TSPO level <0.95, a TSPO level >=0.95 was associated with a higher occurrence of unfavorable outcomes (OR=74.8, 95% CI 1.9- 287.7, p=0.047) (Table V).

To determine whether TSPO is a reliable biomarker for predicting the prognosis of TBI, receiver operating characteristic (ROC) curve, calibration curves and plotted decision curves were performed. The results showed that the AUC, specificity, and sensitivity of TSPO were 0.88, 0.82, and 0.88 respectively. The calibration curves showed that the predicted outcome fit well to the observed outcome (p=0.218). The decision curves showed that the patients could achieve benefits if the threshold probability was >5% and <70%. The results above indicated that TSPO is a reliable biomarker for predicting the prognosis of TBI (Table VI) (Figure 4A-C).

DISCUSSION

TBI is one of the main causes of disability and mortality. The mechanism underlying TBI is complicated due to its heterogeneous nature. As TBI research has advanced, it has been demonstrated that the pathophysiology of TBI is associated with not only the primary injury, but also secondary injuries caused by the neuroinflammatory response, apoptosis,

Table III: The Relationship of Covariates and Outcome

Covariates	β	OR (95%CI)	p
ICP (mmHg)	0.18	1.19 (1.10, 1.30)	<0.0001
Time to operating room (h)	0.65	1.91 (1.15, 3.18)	0.0124
Helsinki CT score	0.77	2.17 (1.53, 3.07)	<0.0001
Age (year)	-0.0054	0.99 (0.96, 1.03)	0.7749
Sex	0.43	1.54 (0.62, 3.85)	0.3533
GCS	-0.89	0.41 (0.08, 1.99)	0.2680
Body mass index (kg/m²)	-0.088	0.92 (0.79, 1.06)	0.2479
Diabetes	0.48	1.62 (0.58, 4.49)	0.3552
Hyperlipidemia	0.22	1.24 (0.49, 3.11)	0.6419
SBP (mmHg)	0.019	1.02 (0.99, 1.04)	0.0527
DBP (mmHg)	-0.015	0.98 (0.95, 1.01)	0.3245
Hyperlipidemia	0.58	1.79 (0.46, 6.94)	0.4012

Table IV: The Covariables Filtered with Two Criterions

Criterion 1	Criterion 2
ICP, Helsinki CT score, Body mass index, SBP, Hyperlipidemia	ICP, Time to operating room, Helsinki CT score, Body mass index, SBP, Hyperlipidemia

Criterion 1: *The effect on the regression coefficient of outcome>10%*
Criterion 2: *The p value of regression coefficient of outcome <0.1*

Table V: Relationship Between TSPO and Outcome

Outcome	Crude model		Model I		Model II	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
TSPO	4.8 (2.5, 9.2)	<0.001	5.5 (2.7, 10.9)	<0.001	12.0 (1.5, 93.2)	0.018
TSPO group						
<0.95	Reference		Reference		Reference	
>=0.95	13.1 (3.6, 48.3)	<0.001	13.1 (3.5, 48.5)	<0.001	74.8 (1.9, 287.7)	0.047

Crude model adjust for: *None;* ***Model I adjust for:*** *age; sex;* ***Model II adjust for:*** *ICP, Time to operating room, Helsinki CT score, Body mass index, SBP, Hyperlipidemia.*

Table VI: ROC Analysis Results

Items	AUC	Accuracy	Specificity	Sensitivity	PLR	NLR	DOR
TSPO	0.88	0.84	0.82	0.88	4.79	0.14	33.86

AUC: *Area under the curve,* ***PLR:*** *Positive likelihood ratio,* ***NLR:*** *Negative likelihood ratio,* ***DOR:*** *Diagnostic odds ratio.*

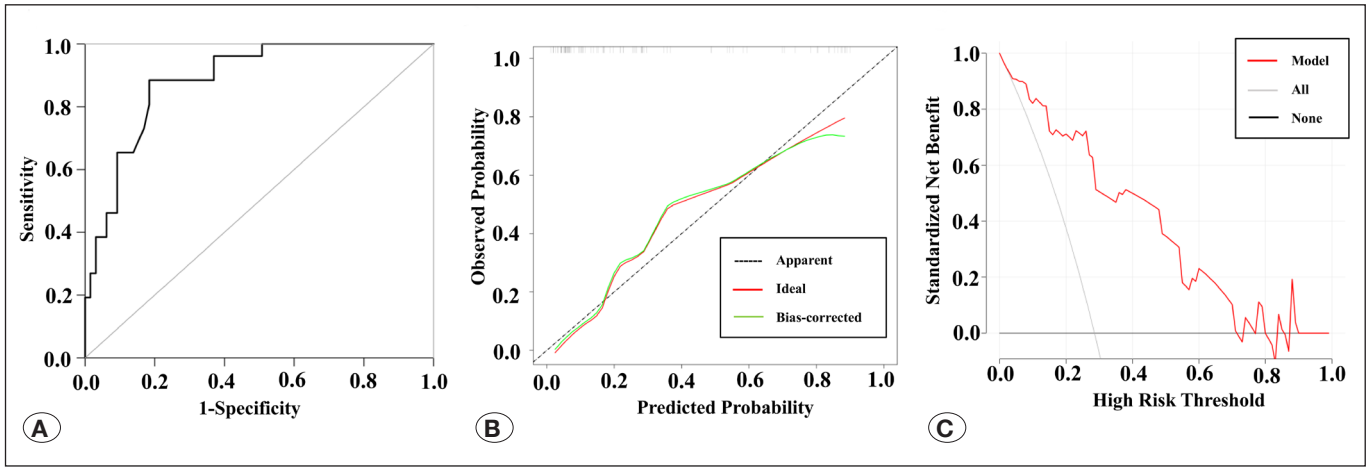

Figure 4: The assessment of TSPO for the prognosis of TBI. The ROC analysis showed that the AUC of TSPO was 0.88 **(A)**. The calibration curves showed that the predicted outcome fitted well to the observed outcome (p=0.218) **(B)**. The decision curves showed the patients could achieve benefits if the threshold probability is >5% and <70% **(C)**.

and the development of edema (10,16,19,30). Consequently, it is difficult to predict the prognosis of TBI. Previous studies have showed that there are differences in the ICP, GCS, and CT classification in TBI patients with different outcomes (1, 24). In our study, we also observed a significant correlation between CT classification, ICP, time to the operating room and TBI outcome by univariate regression analysis. However, as previously proven, the factors above were not sufficiently reliable to predict the outcome of TBI (1).

An increasing number of studies have shown that several biomarkers may predict the outcome of TBI. In recent decades, several studies have proven that a series of biomarkers, including phospho-Tau, GFAP, S100B, and NSE, represent postinjury neurodegeneration, astroglia injury or neuronal cell body injury (10,19,30). However, validation of the prognostic utilities of these biomarkers have been slow. Consequently, it is necessary to discover more biomarkers for predicting patient outcome. Recently, it was reported that serum TSPO expression was associated with the outcome of patients with TBI and acute ischemic stroke (4,15). However, few studies have focused on the expression of TSPO in TBI patient brain tissue. In our study, we found that the expression of TSPO in the unfavorable outcome group was higher than that in the favorable outcome group. Double immunofluorescence staining showed that TSPO was expressed mainly in microglia, which is consistent with previous studies. The results above implied that TSPO may be a biomarker for predicting the prognosis of TBI.

TSPO participates in multifarious cellular functions, including mitochondrial respiration, apoptosis, and cell proliferation

(3,17). Positron emission tomography (PET) has been used to determine TSPO expression in the animal and human brain. PET have shown that TSPO expression is low in the healthy brain and upregulated in the injured brain. The increased expression of TSPO in microglia demonstrated that TSPO may be a factor influencing the progression of TBI (18,31). Previous studies have shown that the TSPO ligands, PK-11195 and Ro5-4864, are important for TBI treatment through antiapoptotic effects (9,21,25,29). Soustiel et al. recently showed that Ro5-4864 significantly increased the number of surviving neurons by reducing the activation of caspase 3 in TBI rat models (21,25). Previous studies have implied that TSPO plays an important role in TBI and may be a biomarker for outcome. In our study, we found that each 1-unit increase in TSPO expression was associated with a 40% higher occurrence of unfavorable outcomes after adjusting for all confounding factors such as initial GCS, ICP, time to the operating room and Helsinki CT classification. Moreover, ROC analysis also proved that TSPO was a reliable biomarker for predicting the prognosis of TBI.

The results of the present study are only preliminary. The main limitation of this study is its small sample size, consequently the predictive effect was susceptible to bias. Secondly, we only gathered brain samples from serious TBI patients who needed surgical treatment, which may affect the prognostic assessment. Therefore, in further studies, multiple brain samples should be collected to assess the role of TSPO in predicting the prognosis of TBI. Moreover, as previous studies have shown, multitudinous factors can influence the outcome of TBI. Consequently, in new studies to determine biomarkers for predicting the outcome of TBI, we should adjust for more variables to improve the reliability.

CONCLUSION

In our study, we established models for predicting TBI outcomes and found that higher TSPO expression was associated with a higher occurrence of unfavorable outcomes. Moreover, TSPO was a reliable biomarker for predicting the prognosis of TBI.

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AUTHORSHIP CONTRIBUTION

Study conception and design: WJ

Data collection: XY

Analysis and interpretation of results: QB

Draft manuscript preparation: QB

Critical revision of the article: WJ

Other (study supervision, fundings, materials, etc...): XB, WW, PJ

All authors (QB, XY, XB, WW, PJ, WJ) reviewed the results and approved the final version of the manuscript.

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