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RESEARCH ARTICLE

Effects of apolipoprotein E polymorphism on cerebral oxygen saturation, cerebral perfusion, and early prognosis after traumatic brain injury

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Abstract

Objective: To investigate the effects of the apolipoprotein E (APOE) gene on oxygen saturation and cerebral perfusion in the early stages of traumatic brain injury (TBI). **Methods**: This study included 136 consecutive TBI patients and 51 healthy individuals. The APOE genotypes of all subjects were determined using quantitative fluorescence polymerase chain reaction (QF-PCR). Regional cerebral oxygen saturation (rScO2) of patients with TBI and normal subjects was monitored using near-infrared spectroscopy (NIRS). Computed tomography (CT) perfusion was used to obtain cerebral perfusion in patients with TBI and normal subjects. **Results**: In the TBI group, the rScO2 of APOEε4 carriers (53.06 ± 6.87%) was significantly lower than that of non-carriers (58.19 ± 5.83%, $p < 0.05$). Meanwhile, the MTT of APOEε4 carriers (6.75 ± 1.30 s) was significantly longer than that of non-carriers (5.87 ± 1.00 s, $p < 0.05$). Furthermore, correlation analysis showed a negative correlation between rSCO2 and MTT in patients with TBI. Both the univariate and multifactorial logistic regression analyses revealed that APOE ε4, hypoxia, MTT >5.75 s, Marshall CT Class, and GCS were independent risk factors for early poor prognosis in patients with TBI. **Conclusion**: Both cerebral perfusion and cerebral oxygen were significantly impaired after TBI, and low cerebral perfusion and hypoxia were related to poor prognosis of patients with TBI. Compared with APOE ε4 non-carriers, APOE ε4 carriers not only had poorer cerebral perfusion and cerebral oxygen metabolism but also worse prognosis in the early stages of TBI. Furthermore, a negative correlation was observed between the rSCO2 and MTT levels. In addition, both CT perfusion scanning (CTP) and NIRS are reliable for monitoring the condition of patients with TBI in the neurological intensive care unit (NICU).

Introduction

Traumatic brain injury (TBI) is a substantial injury to the brain tissue that can temporarily or permanently impair brain function. It is one of the most common emergencies in the central nervous system (CNS), with high morbidity and mortality, causing disastrous consequences to families and a huge burden on the health care resources of the whole society.[1] Most patients with TBI require observation and treatment in the neurosurgery intensive care unit (NICU)[2,3] because of their complicated and unstable conditions. Therefore, many methods are used to monitor all kinds of indices in patients with TBI, which are useful not only for evaluation but also for prediction of the patients' conditions.

Previous studies have shown that patients with TBI carrying APOE ε4 may have poorer prognosis.[4,5] We also found that among TBI patients, APOE ε4 carriers had lower cerebral oxygen saturation than APOE ε4 non-carriers.[6] Furthermore, compared to APOE ε4 non-carriers, APOE ε4 carriers had a higher frequency of abnormal slow waves in the EEG at the early stage of

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TBI.[7] These results suggest that abnormal local cerebral oxygen and brain electrical activity may be related to the negative effect of APOE ε4 on the prognosis of patients with TBI. Both cerebral oxygen metabolism and brain electrical activity are closely associated with cerebral blood perfusion, which are also considered important indices for evaluating the condition of TBI patients.[6,8] Among the methods used to measure cerebral blood perfusion,[9] computed tomography perfusion (CTP) is one of the most commonly used methods, providing a convenient and reliable assessment of cerebral circulation and perfusion in TBI patients.[10]

In the present study, we aimed to explore the changes in cerebral blood perfusion using CTP and study the effects of different APOE subtypes on cerebral blood perfusion in the early stage of TBI. Furthermore, the relationships between cerebral blood perfusion, cerebral oxygen metabolism, and prognosis of patients with TBI were analyzed.

Materials and Methods

Subjects

This retrospective study complied with the ethical standards established by the Ethics Committee of the First Affiliated Hospital of the Chongqing Medical University. The participants included in this study were admitted between March 2019 and January 2022. Written informed consent was obtained from the patients and their legal guardians for healthy individuals and those who were conscious and cooperative. Written informed consent was obtained from the legal guardians of comatose patients.

All patients with TBI were treated according to the guidelines of TBI treatment.[11,12] The inclusion criteria for TBI patients were a clear history of head injury, age 15–65 years, and hospitalization time of less than 8 h after injury. The exclusion criteria were: (i) serious scalp injury, subcutaneous hematoma, or skull fracture injury affecting the monitoring of cerebral oxygen saturation; (ii) a medical history of CNS diseases (such as past medical history of cerebrovascular disease, brain tumor, TBI, encephalitis, dementia or psychosis, Parkinson's disease, demyelinating disease, epilepsy, or abnormal brain development); and (iii) use of drugs or treatments that might affect cerebral perfusion and cerebral oxygen saturation.

The inclusion criterion for normal volunteers was normal individuals aged 15–65 years old with no history of TBI. The exclusion criteria were (i) neurological disorders (e.g., cerebrovascular disease, intracranial occupying lesions, encephalitis, psychosis, or dementia); (ii) respiratory and circulatory disorders that severely affect cerebral oxygen saturation and cerebral perfusion; and (iii) use of medications or treatments that might affect cerebral oxygen saturation and cerebral perfusion.

CTP screening protocol

All patients with TBI accepted CTP within 24 h after injury. Briefly, the head was scanned from bottom to top using a Lightspeed VCT 64-row CT machine with turcica selected as the basal layer. The specific parameters were as follows: slice thickness, 5 mm; tube voltage, 80 V; and tube current, 200 mA. Adw4.2 workstation was used to process all scanned raw images. In this study, the anterior cerebral artery was used as the input artery and the superior sagittal sinus was used as the output vein. The frontal, temporal, occipital, parietal, thalamic, and basal ganglia of the lateral and contralateral mirror regions were scanned as regions of interest (ROI). CTP parameters, including mean transmission time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV) were calculated. The parameters and CTP maps were then analyzed by two experienced, blinded radiologists.

Monitoring of $rScO_2$

In this study, $rScO_2$ was monitored using a minR-P100 non-invasive cerebral oxygen monitor (Chongqing Mingxi Medical Instrument Co., Ltd.). For patients with TBI, $rScO_2$ was monitored using NIRS–1–3 days after injury. The patient's $rScO_2$ was also monitored using NIRS as soon as the patient's condition changed. For healthy people, $rScO_2$ was monitored using NIRS in a relaxed and awake setting.[13–15] The forehead was exposed and cleaned, and the probe was tightly connected and fixed to the forehead skin bilaterally. The probe was positioned 1–2 cm from the upper edge of the eyebrow arch. The $rScO_2$ data were then analyzed and collected. The mean monitoring time per patient was 30 min, and the mean $rScO_2$ value was obtained using an NIRS machine.

Identification of APOE genotype

Venous blood samples were collected from all subjects and labeled for further use. The APOE genotypes of all subjects were determined using quantitative fluorescence polymerase chain reaction (QF-PCR), and all participants were classified as APOE ε4 carriers or non-carriers based on whether the APOE ε4 allele was present in the tested genotype.[16]

Data processing and analysis

SPSS software (Windows version 26.0, IBM Corporation, Armonk, NY, USA) was used for the data analysis and

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statistical processing. The Student's *t*-test was used to examine differences in $rScO_2$ and CTP data between carriers and non-carriers, and the chi-square test or Mann–Whitney U-test was used to compare differences in clinical data and other categorical outcomes between the two types of subjects. Correlation analysis was used to investigate the correlation between cerebral oxygen saturation and cerebral perfusion in TBI patients. Logistic regression analysis was used to analyze potential risk factors for the early prognosis of patients with TBI. MedCalc (Windows version 20.100) was used to plot the ROC curves. Statistical significance was set at $p < 0.05$.

Results

A total of 152 TBI patients and 58 healthy individuals participated in this study. However, 16 patients and seven healthy individuals were excluded based on the exclusion criteria. In total, 136 consecutive patients and 51 healthy individuals were included in this study. The APOE genotype (APOEε2/ε3/ε4) and allele frequencies of all subjects complied with the Hardy–Weinberg law. All subjects were divided into APOE ε4 carrier and non-carrier groups based on the presence or absence of the ε4 allele. The general clinical data of the two groups were analyzed and indicated no statistical significance (Tables 1–4). The GOS score was used to evaluate the early prognosis (2 weeks after admission) of TBI patients, defining patients with scores of 1, 2, and 3 as having a poor early prognosis, and those with scores of 4 and 5 as having a good early prognosis. After statistical analysis, 107 patients (78.68%) had a good early prognosis and 29 patients (21.32%) had a poor early prognosis.

The association between APOE and the early prognosis of TBI patients

In the TBI group, 48% of APOE ε4 carriers had a good early prognosis (GOS 4–5), and 52% of APOE ε4 carriers had a poor early prognosis (GOS 1–3). Among APOE ε4 non-carriers, patients with TBI (14.41%) had a poor early prognosis (GOS 1–3), which was significantly lower than that of APOE ε4 carriers ($p < 0.001$, Table 5). According to our study, the OR of unfavorable outcomes in APOE ε4 carriers was greater than that in other relevant studies[4,5] Thus, in TBI patients, the early prognosis of those carrying APOE ε4 might be worse than that of non-carriers. A previous study also showed that APOE ε4 does not have a significant effect on the prognosis of TBI patients.[17] This differs from the results of the present study. This may be because our study had a small sample size and was a single-center clinical study with statistical limitations. Therefore, multicenter studies with large sample sizes are needed to further validate our findings.

Table 1. APOE genotypes and allele frequencies in the TBI group and the normal group.

	Genotype (*n*)						Allele frequency (%)		
Group	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4	ε2	ε3	ε4
TBI group (*n* = 136)	4	15	5	92	16	4	10.29	79.04	10.67
Normal group (*n* = 51)	2	3	2	37	5	2	8.82	80.39	10.79

APOE, apolipoprotein E; TBI, traumatic brain injury.

Table 2. Comparison of characteristics in normal group.

Items	APOE ε4 non-carriers (*n* = 42)	APOE ε4 carriers (*n* = 9)	*p*
Sex			0.503
Male	20	6	
Female	22	3	
Alcohol-drinking			0.309
Yes	13	5	
No	29	4	
Smoking			0.287
Yes	17	6	
No	25	3	
Hypertension			1.000
Yes	15	3	
No	27	6	
Heart disease			1.000
Yes	9	2	
No	33	7	
Hemoglobin (g/L)			0.283
<120	7	3	
120–150	26	3	
>150	9	3	
Age			0.346
<45	9	4	
45–60	17	2	
>60	16	3	

APOE, apolipoprotein E.

The association between APOE and CTP results at the early stage of TBI

The mean MTT of TBI patients was 6.03 ± 1.11 s, which was significantly longer than that of the normal group (4.36 ± 0.82 s, $p < 0.001$). In the normal group, no significant difference in MTT was found between APOE ε4 carriers and non-carriers (4.28 ± 0.86 s vs. 4.38 ± 0.83 s,

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Table 3. Comparison of clinical data between APOE ε4 carriers and non-carriers in TBI group.

Items	APOE ε4 non-carriers (n = 111)	APOE ε4 carriers (n = 25)	p	df
Age			0.061	5.608
<45	31	13		
45–60	47	8		
>60	33	4		
Sex			0.247	1.339
Male	63	17		
Female	48	8		
Alcohol-drinking			0.616	0.252
Yes	55	11		
No	56	14		
Smoking			0.568	0.326
Yes	42	11		
No	69	14		
Hypertension			0.426	0.633
Yes	48	13		
No	63	12		
Heart disease			0.602	0.272
Yes	65	16		
No	46	16		
Hemoglobin (g/L)			0.068	1.520
<120	27	12		
120–150	41	8		
>150	43	5		

APOE, apolipoprotein E; TBI, traumatic brain injury.

Table 4. GCS information and CT scan between APOE ε4 carriers and non-carriers in TBI group.

Items	APOE ε4 non-carriers	APOE ε4 carriers	p	df
GCS			<0.001	16.074
3–8	12	11		
9–12	31	5		
13–15	68	9		
Marshall CT class			0.020	13.437
I (normal CT)	12	1		
II (cisterns present, shift <5 mm)	20	1		
III (cisterns compressed, shift <5 mm)	40	10		
IV (shift >5 mm)	30	5		
V (evacuated mass)	6	5		
VI (non-evacuated mass)	3	3		

APOE, apolipoprotein E; TBI, traumatic brain injury.

Table 5. The prognosis of APOE ε4 carriers and non-carriers in TBI group.

Group	APOE ε4 non-carriers	APOE ε4 carriers	p
GOS (1–3)	16	13	<0.001
GOS (4–5)	95	12	

APOE, apolipoprotein E; GOS, Glasgow Outcome Scale; TBI, traumatic brain injury.

$p > 0.05$). However, in the TBI group, the mean MTT of APOE ε4 carriers was 6.75 ± 1.30s, which was significantly longer than that of non-carriers (5.87 ± 1.00s, $p < 0.001$), suggesting that the APOE ε4 allele may be related to the impaired cerebral perfusion at the early stage of TBI (Fig. 1).

To determine the proper threshold of MTT to determine the level of cerebral perfusion, we plotted the subject's operating characteristic curve (ROC curve, Fig. 2). The maximum Jorden index was calculated to be 0.34 when MTT was >5.75 s, which corresponds to a sensitivity of 50.00% and specificity of 84.04% (AUC = 0.700, $p < 0.001$). Therefore, this study defined MTT >5.75 s as high-risk for impaired perfusion, which meant patients with MTT >5.75 s were more likely to have impaired perfusion and were included in the high-risk group, while patients with MTT >5.75 s were included in the low-risk group. As shown in this study, the proportion (56%) of APOE ε4 carriers with impaired perfusion was

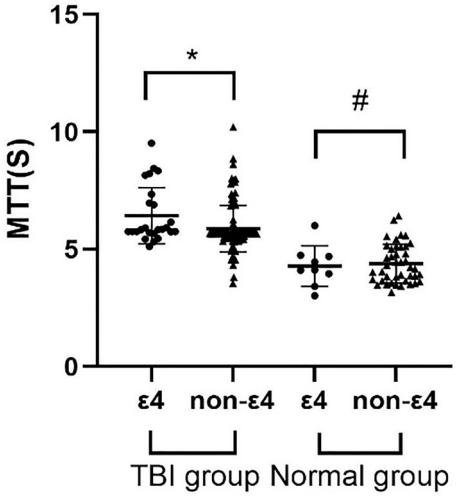

Figure 1. The MTT of APOE ε4 carriers in the TBI group was statistically significantly longer than that of APOE ε4 non-carriers (*$p < 0.05$). However, the MTT of APOE ε4 carriers in the normal group did not show a significant difference compared with APOE ε4 non-carriers ($^{\#}p > 0.05$).

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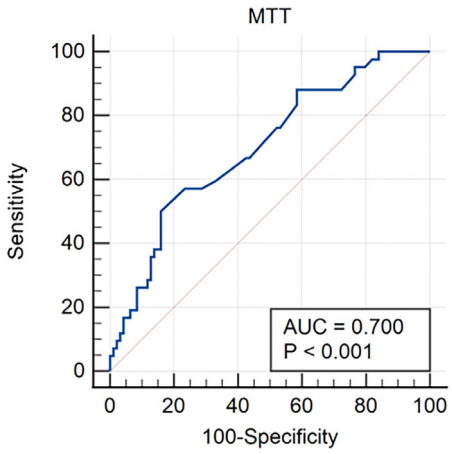

Figure 2. ROC curve for MTT.

Table 6. The mean MTT of APOE ε4 carriers and APOE ε4 non-carriers in TBI group.

Items	APOE ε4 non-carriers	APOE ε4 carriers	*p*
MTT (s)	5.87 ± 1.00	6.75 ± 1.30	<0.001
High risk (qty)	22	14	<0.001

APOE, apolipoprotein E; High risk, MTT >5.75 s defined as high risk; MTT, mean transit time; TBI, traumatic brain injury.

significantly higher than that of APOE ε4 noncarriers (18.92%) ($p < 0.05$, Table 6, Fig. 2).

The association between APOE and NIRS results at the early stage of TBI

The mean $rScO_2$ of TBI patients was 56.89 ± 6.07%, which was significantly lower than that of the normal group (67.28 ± 6.38%, $p < 0.001$), indicating that $rScO_2$ was significantly decreased in TBI patients. The mean $rScO_2$ of APOE ε4 carriers in the TBI group was 53.57 ± 6.49%, which was remarkably lower than that of APOE ε4 non-carriers (57.63 ± 5.74%), indicating statistical significance ($p < 0.05$) (Table 7, Fig. 3).

In our previous research, $rScO_2$ below 55% was considered to be hypoxia,[6] while $rScO_2$ >55% was considered non-hypoxic. The hypoxia rate of APOE ε4 carriers was

Table 7. The mean $rScO_2$ of APOE ε4 carriers and non-carriers in TBI group.

Items	APOE ε4 non-carriers	APOE ε4 carriers	*p*
$rScO_2$ (%)	58.19 ± 5.83	53.06 ± 6.87	<0.001
Hypoxia (qty)	24	13	0.002

APOE, apolipoprotein E; Hypoxia, $rScO_2$<55% defined as hypoxia; $rScO_2$, regional cerebral oxygen saturation; TBI, traumatic brain injury.

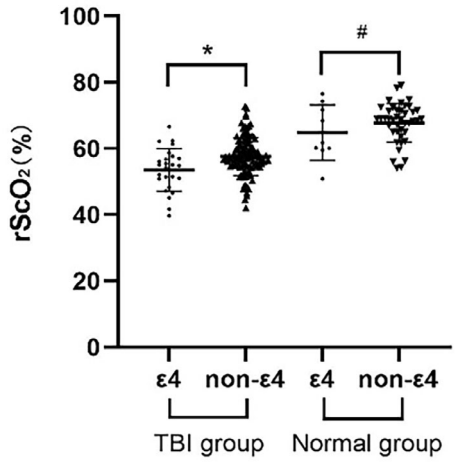

Figure 3. The rScO2 of APOE ε4 carriers in the TBI group was significantly lower than that of APOE ε4 non-carriers, which was statistically significant (*$p < 0.05$). However, the rScO2 of APOE ε4 carriers in the normal group did not show a significant decrease compared with APOE ε4 non-carriers ($^{\#}p > 0.05$).

up to 52% (13/25) in the TBI group, which was significantly higher than that of APOE ε4 non-carriers (21.62%) (24/111, $p < 0.05$).

The association between CTP and NIRS results at the early stage of TBI

The correlation analysis of $rSCO_2$ and MTT in TBI patients showed a negative correlation between the two parameters ($r = -0.740$, $p < 0.001$), indicating that $rSCO_2$ decreased as the MTT increased (Fig. 4).

The association among APOE, CTP and cerebral oxygen saturation, and the early prognosis of TBI patients

Of the four APOE ε4 pure individuals, two had a better prognosis and two had a worse prognosis. Individual 1

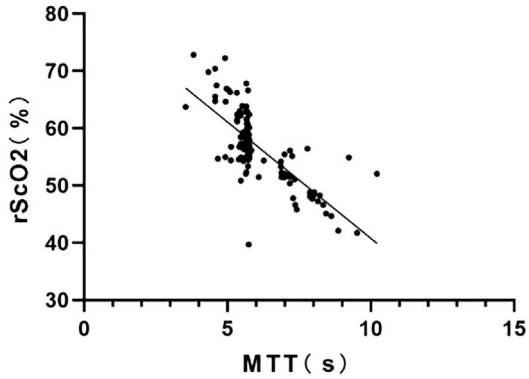

Figure 4. In TBI patients, MTT was negatively correlated with rSCO2.

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had 51.06% rScO2 and 7.34 s MTT, individual 2 had 52.11% rScO2 and 6.97 s MTT, individual 3 had 54.19% rScO2 and 6.86 s MTT, and individual 4 had 57.72% rScO2 and 5.75 s MTT. As shown in Tables 8 and 9, one-way logistic regression analysis showed that hypoxia, APOE ε4, MTT >5.75 s, Marshall CT Class, and GCS

Table 8. Independent risk factors affecting prognosis in the TBI group by single-factor and multi-factor logistic regression analysis.

Items	GOS (1–3) (*n* = 29)	GOS (4–5) (*n* = 107)	Single-factor l ogistic regression *p*	Multi-factor logistic regression analysis *p*	OR (95% CI)
Sex			0.926		
Male	16	58			
Female	13	49			
Age			0.751		
<45	10	34			
45–60	10	45			
>60	9	28			
Genotype			<0.001	0.015	6.299 (1.4272–7.810)
APOE ε4 carriers	13	12			
APOE ε4 non-carriers	16	95			
Injury mechanism			0.207		
Striking injury	10	25			
Traffic injury	13	42			
Falling or others	8	40			
GCS			0.006	0.044	2.477 (1.025–5.991)
3–8	10	13			
9–12	3	33			
13–15	16	61			
Marshall CT class			<0.001	0.016	1.932 (1.130–3.304)
I (Normal CT)	1	12			
II (cisterns present, shift <5 mm)	2	19			
III (cisterns compressed, shift <5 mm)	7	43			
IV (shift >5 mm)	9	26			
V (evacuated mass)	4	7			
VI (non-evacuated mass)	6	0			
Smoking			0.466		
Yes	13	40			
No	16	67			
Alcohol-drinking			0.198		
Yes	11	55			
No	18	52			
Hypertension			0.672		
Yes	12	49			
No	17	58			
Heart disease			0.329		
Yes	7	36			
No	22	71			
Hemoglobin (g/L)			0.270		
<120	11	28			
120–150	7	42			
>150	11	37			
$rScO_2$			<0.001	0.011	8.675 (1.651–45.582)
Hypoxia	24	23			
Non-hypoxia	5	84			
MTT			<0.001	0.006	9.926 (1.938–50.827)
High risk	23	13			
Low risk	6	94			

95% CI, 95% confidence interval; APOE, apolipoprotein E; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; high risk, MTT >5.75 s defined as high risk; Hypoxia, $rScO_2$<55% defined as hypoxia; MTT, mean transit time; OR, odds ratio; TBI, traumatic brain injury.

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Table 9. Multi-factor logistic regression model.

	Model 1		Model 2		Model 3		Model 4		Model 5	
Items	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sex	1.763#	0.639, 4.858	1.134#	0.362, 3.556	1.184#	0.366, 3.833	1.738#	0.614, 4.919	1.764#	0.592, 5.256
Age	1.607#	0.816, 3.167	1.140#	0.552, 2.358	0.999#	0.458, 2.180	1.603#	0.813, 3.161	1.339#	0.676, 2.882
Genotype	8.580*	2.986, 24.651	7.416*	2.092, 26.282	3.689*	1.032, 13.192	8.370*	2.689, 26.049	5.883*	1.875, 18.458
$rScO_2$			17.655*	5.508, 56.597						
MTT					22.520*	7.346, 69.042				
GCS							0.965#	0.525, 1.774		
Marshall CT class									2.084*	1.342, 3.237

95% CI, 95% confidence interval; APOE, apolipoprotein E; GCS, Glasgow Coma Scale; MTT, mean transit time; OR, odds ratio; $rScO_2$, regional cerebral oxygen saturation; TBI, traumatic brain injury.
*$p < 0.05$;
#$p > 0.05$.

were independent risk factors for poorer prognosis after TBI. At the same time, multi-factor logistic regression analysis showed that APOE ε4, hypoxia, MTT >5.75 s, Marshall CT Class, and GCS were independent risk factors for poor prognosis in early TBI.

Discussion

The main result of the study was that APOE ε4 carriers not only had significantly lower cerebral perfusion and cerebral oxygen saturation, but also had significantly worse outcomes than APOE ε4 non-carriers at the early stage of TBI.

As shown by CTP, the mean MTT in the TBI group was 6.03 ± 1.11 s, which was significantly longer than that of the normal group (4.36 ± 0.82 s, $p < 0.001$), indicating that cerebral perfusion was significantly impaired after TBI. Furthermore, the mean MTT of APOE ε4 carriers at the early stage of TBI was 6.75 ± 1.30s, which was significantly longer than that of non-carriers (5.87 ± 1.00s, $p < 0.001$). However, no significant difference in the MTT was found between APOE ε4 carriers and non-carriers in the normal group. This indicated that cerebral perfusion of APOE ε4 carriers was significantly impaired at the early stage of TBI, which also suggested that the harmful effects of APOE ε4 on cerebral perfusion usually occur in TBI patients but not in normal people. Previous studies have shown that APOE ε4 may be related to the development of cerebral hypoperfusion after TBI.[18] APOE ε4 may disrupt the blood–brain barrier (BBB) by influencing the NF-κB/MMP-9 pathways and inhibiting BBB repair after TBI.[18–20] Therefore, both effects of APOE ε4 on the BBB might cause cerebral perfusion disorder and finally lead to cerebral hypoperfusion.

Three parameters are usually available in CT perfusion scans of the brain: CBV, CBF, and MTT (CBV=CBF × MTT). MTT is calculated through a deconvolution operation, which is relatively robust and is considered the mean time for the blood to cross the capillary network. Furthermore, in studies on cerebral perfusion, MTT is considered a sensitive parameter for the early detection of perfusion defects.[21,22] In addition, MTT is less affected by gray and white matter differences and has been shown to be the most reproducible.[21,23] Therefore, in this study, MTT was chosen as the parameter to evaluate cerebral perfusion in patients with TBI.

In the TBI group, the mean $rScO_2$ of APOE ε4 carriers was 53.57 ± 6.49%, which was significantly lower than that of APOE ε4 non-carriers (57.63 ± 5.74%, $p < 0.001$). This finding is consistent with the results of our previous study.[7] Furthermore, based on the correlation analysis, there was a negative link between the patient's MTT and $rScO_2$, indicating that cerebral oxygen saturation decreased in the presence of poorer cerebral perfusion.[24] Previous studies have shown that maintaining the stability of cerebral blood perfusion and cerebral oxygen metabolism after TBI is crucial for the recovery of brain function,[6,25] and weakened cerebral blood perfusion and destruction of cerebral oxygen metabolism may lead to a poor prognosis in patients with TBI.[26] Moreover, studies on the cerebral cortex have shown that decreased cerebral perfusion might cause a decrease in the amount of oxygen available to brain tissue.[27,28] Therefore, impaired cerebral perfusion and cerebral oxygen metabolism may subsequently lead to poor neurological function and prognosis in patients with TBI, which is consistent with the results of the present study.

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In the TBI group, the mean GOS of APOE ε4 carriers was significantly higher than that of APOE ε4 non-carriers, suggesting that APOE ε4 carriers were more likely to have worse outcomes than APOE ε4 non-carriers after TBI, which is also consistent with our previous studies.[6,7,18,29]

Previous studies have also shown that patients with poorer cerebral perfusion usually have a worse prognosis, while cerebral oxygen saturation was also reported to be related to prognosis after TBI.[16,19,30,31] However, the associations between cerebral perfusion, cerebral oxygen saturation, and TBI prognosis remain unclear. As shown in the present study, both MTT and $rScO_2$ levels were significantly impaired in the early stages of TBI. Moreover, a negative correlation was found between the MTT and $rScO_2$, suggesting that the decrease in cerebral perfusion in a patient may also be followed by a decrease in cerebral oxygen saturation. The results of logistic regression analysis showed that APOE ε4, hypoxia, and MTT >5.75 s were risk factors for the poor prognosis of TBI patients, which was also consistent with the findings of our previous study.[6,7,32] Therefore, APOE ε4 carriers in the TBI group had not only a longer MTT and poorer $rScO_2$ but also a lower GOS compared to non-carriers.

Previously, we have shown that APOE plays an important role in secondary brain injury, which is crucial for prognosis after TBI. Unlike APOE ε2 and ε3, APOE ε4 showed negative effects on the balance of calcium and excited amino acids, inflammatory response, and apoptosis, which might cause impairment of blood–brain barrier (BBB) permeability.[6,7,18,19,33,34] Therefore, we speculate that APOE ε4 leads to a disorder in cerebral perfusion and cerebral oxygen metabolism by impairing BBB permeability, which ultimately influences the prognosis of TBI.

Although the results of this study are promising, we acknowledge that it has some limitations. NIRS and CTP have several limitations when used as methods for evaluating cerebral oxygen saturation and cerebral perfusion. First, NIRS reflects the corresponding changes, not the absolute value of $rScO_2$, and the interpretation of the NIRS results may be influenced by the experience of the operators. In addition, CTP is associated with adverse reactions to ionizing radiation and iodine contrast agents. In addition, this was a small sample and single-center clinical study, and this has statistical limitations. Therefore, a large-scale sample and multiple-center study are needed for further verification.

Conclusion

After TBI, both cerebral perfusion and oxygen levels were significantly impaired. Compared with APOE ε4 non-carriers, APOE ε4 carriers not only had poorer cerebral perfusion and cerebral oxygen metabolism but also worse prognosis in the early stages of TBI. Furthermore, there was a positive correlation between cerebral perfusion and cerebral oxygen saturation, and both low cerebral perfusion and cerebral hypoxia were related to a poor prognosis of patients with TBI. In addition, both CTP and NIRS can provide reliable and convenient methods for monitoring and assessing the condition of patients with TBI in the NICU.

Author Contributions

All authors contributed to the successful completion of this study. This study was designed and conducted by Xie et al. Material preparation, data collection and analyses were performed by Xun Lin, Yulong Xia, Li Jiang and Yanfeng Xie. Xun Lin, Li Jiang wrote the first draft of this manuscript. All authors made comments and suggestions on the previous editions of the manuscript. The final manuscript was approved after all authors had read it to their satisfaction.

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Conflict of Interest

None of the authors of this article has a competing interest to declare.

Ethics Approval

This study was designed based on the guidelines for human studies approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, and it was ethically in accordance with the Helsinki Declaration.

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Consent to Participate

Informed consent was obtained from all the study participants.

Consent for Publication

Written consent was obtained from the parents or legal guardians of all study participants.

Code Availability

Not applicable.

Data Availability Statement

Data supporting the findings of this research are available on request owing to privacy and ethical restrictions.

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