Article

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Correlation between the Degree of Inflammation and Stress Indicators and Concurrent Cognitive Impairment in Patients with Severe Craniocerebral Injury

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Abstract

Background: Craniocerebral injuries can cause inflammation and oxidative stress, and can have permanent effects on cognitive function. Moreover, over time, excessive expression of inflammatory factors and high levels of oxidative stress will be detrimental to recovery from craniocerebral injury and may exacerbate neurological damage, further damaging neurons and other cellular structures. In this study, we investigated changes in inflammation and stress indicators in patients with severe craniocerebral injuries, and analyzed associations with concurrent cognitive impairment.

Methods: 82 patients with severe craniocerebral injuries admitted to Longyou County People's Hospital during January 2022–June 2023 were selected for retrospective study. Levels of inflammatory factors and the degree of oxidative stress were recorded and compared between the acute and chronic phases. Inflammatory measures included interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP), and oxidative stress indicators included human cortisol (Cor), norepinephrine (NE), and superoxide dismutase (SOD). The patients' cognitive function was evaluated using the Mini-Mental State Examination (MMSE), and the incidence of cognitive impairment was assessed. Spearman's correlation was used to analyze associations between inflammatory and oxidative stress measures and MMSE scores; logistic regression was used to analyze the related factors affecting the patients' concurrent cognitive impairment; and the receiver operating characteristic (ROC) curve was used to test the predictive value of inflammatory and oxidative stress measures on the patients' concurrent cognitive impairment in the acute phase and the chronic phase.

Results: Patients had higher levels of IL-6, IL-10, TNF-α, CRP, Cor, and NE, and lower levels of SOD, in the acute phase compared to the chronic phase ($p < 0.05$). MMSE scores were higher in the acute phase than in the chronic phase ($p < 0.05$). A total of 50 cases were complicated by cognitive impairment, and the incidence of cognitive impairment was 60.98%. The levels of IL-6, IL-10, TNF-α, CRP, Cor, and NE in the chronic phase were positively correlated with the concurrent cognitive impairment, and the level of SOD was negatively correlated with the concurrent cognitive impairment ($p < 0.05$). Single-factor analysis showed that age and levels of IL-6, IL-10, TNF-α, CRP, Cor, and NE were higher in the cognitively impaired group than in the cognitively normal group, SOD levels were lower than in the cognitively normal group, and percentages of below-secondary school and frontal lobe damage were higher than those in the cognitively normal group ($p < 0.05$). Logistic regression analysis showed that below-secondary school, frontal lobe injury, higher levels of IL-6, IL-10, TNF-α, and CRP in the chronic phase, and lower levels of SOD in the chronic phase were all relevant factors affecting the patients' concurrent cognitive impairment. As shown by the ROC curve, the area under the curve (AUC) for the combination of indicators was 0.949, sensitivity was 0.980, and specificity was 0.844.

Conclusions: The incidence of cognitive impairment is higher in patients with severe craniocerebral injury, and the levels of inflammation and oxidative stress, which are not conducive to recovery, are higher in patients in the acute stage. The risk of concurrent cognitive impairment is higher in patients with a lower level of literacy, frontal lobe injury, and high levels of inflammatory factors and oxidative stress in the chronic stage; these indicators, therefore, have a significant predictive effect on the prognosis of the patients.

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Keywords

critical craniocerebral injury; inflammation; oxidative stress; cognitive impairment

Introduction

Craniocerebral injury refers to a condition in which the head is subjected to an external force that causes damage to the skull, brain tissue, or its surrounding structures. The injury can be categorized as mild, moderate, or severe, and the severity is directly proportional to the severity of the symptoms, which can disrupt the patient's normal brain function and can cause permanent damage to the patient's cognitive, emotional, and physical well-being [1,2]. Brett *et al*. [3] found that when a craniocerebral injury occurs, the central nervous system inflammatory response is activated, and a large number of cytokines and pro-inflammatory mediators are released, resulting in the presence of high levels of inflammatory factors. The limited ability of brain tissues to repair the severe structural trauma results in an inflammatory process that may last for an extended period of time. Related reports show that craniocerebral injury also leads to increased levels of intra- and extracellular oxidative stress, which may cause dysfunction of the body's antioxidant system and lead to lipid peroxidation of cell membranes, protein damage, and DNA damage [4]. Excessive expression of inflammatory factors and higher levels of oxidative stress are detrimental to recovery from craniocerebral injury; therefore, controlling the level of inflammatory response and oxidative stress is of great importance for the treatment and recovery from craniocerebral injury. In addition, craniocerebral injury can lead to serious neuropsychiatric problems and neurodegenerative diseases; notably, cognitive impairment is one of the common complications in patients, and the incidence of cognitive impairment is higher among those with severe craniocerebral injury [5]. Herz *et al*. [6] suggests that high levels of inflammation and oxidative stress after brain injury will increase the risk of patients sustaining neurological damage and may raise the risk of developing cognitive impairment. Therefore, the present study explored changes in inflammatory and stress indicators in patients with severe craniocerebral injury, and analyzed correlations between these indicators and cognitive impairment.

Patients and Methods

Study Design

82 patients with severe craniocerebral injuries admitted to our hospital during January 2022–June 2023 were selected as the study subjects. We were not able to perform sample size calculations due to a lack of identified relevant studies, so we collected as many cases as possible, and initially included a total of 88 patients with severe craniocerebral injuries admitted to our hospital, of which 4 refused to participate in the study and 2 died, resulting in a total of 82 study participants in the final sample. Among the included subjects, 43 cases were male, 39 cases were female, and the average age was (47.07 $\pm$ 3.48) years old. 41 cases were high school and above and 41 cases were below high school in education level. Injuries in 25 cases were due to a fall from height, 53 cases were due to traffic accidents, and 4 cases were injuries from other causes. 44 cases were frontal lobe injuries, 34 cases were craniectomies, and 48 cases were cranial bone repairs. 28 cases had a history of smoking, and 23 cases had a history of drinking alcohol. This study was conducted with the approval and consent of the Longyou County People's Hospital ethics committee (No.202211). All procedures of this study were conducted in accordance with relevant ethical standards such as the Declaration of Helsinki.

Participants

Inclusion criteria: patients were diagnosed with severe craniocerebral injury after clinical examination; patients and their families signed informed consent; patients were hospitalized in our hospital; patients' clinical data were complete and compliance was good; and patients' age was $\geq$18 years. Exclusion criteria: those with malignant tumors; patients transferred halfway through the hospital stay; those with cognitive impairment before hospitalization; those with severe metabolic diseases; those with a history of previous neurological diseases or surgery.

Methods and Assessments

Baseline data: At the time of admission, general data of patients were collected and filed, including gender, age, education level, cause of injury, site of injury, surgical procedure, history of smoking, and alcohol consumption.

Inflammatory factors: Inflammatory factor levels were measured in all patients during the acute phase (1 month after craniocerebral injury) and chronic phase (4 months after craniocerebral injury). Early in the morning of the test day, 5 mL of fasting blood was drawn from the patients, and enzyme-linked immunosorbent assay (ELISA) was used to detect the levels of patients' interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP).

Table 1. Comparison of levels of inflammatory factors and oxidative stress at different times in patients (n = 82).

Indicators	Acute phase	Chronic phase	*t*	*p*
IL-6 (ng/L)	42.86 ± 6.74	21.38 ± 5.15	22.931	<0.001
IL-10 (ng/L)	36.56 ± 5.48	17.23 ± 3.70	26.473	<0.001
TNF-α (ng/L)	37.05 ± 10.12	29.24 ± 6.30	5.933	<0.001
CRP (mg/L)	34.63 ± 8.28	25.72 ± 5.21	8.248	<0.001
Cor (ng/L)	181.74 ± 13.20	142.35 ± 11.25	20.566	<0.001
NE (ng/L)	296.47 ± 22.30	232.36 ± 17.08	20.668	<0.001
SOD (U/mL)	3.11 ± 0.26	3.48 ± 0.37	7.409	<0.001

IL-6, interleukin-6; IL-10, interleukin-10; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein; Cor, cortisol; NE, norepinephrine; SOD, superoxide dismutase.

Table 2. Correlations between the levels of inflammatory factors and oxidative stress and cognitive impairment.

Indicators	Co-occurring cognitive impairment	
	r	*p*
IL-6 (ng/L)	0.300	0.006
IL-10 (ng/L)	0.349	0.001
TNF-α (ng/L)	0.353	0.001
CRP (mg/L)	0.296	0.007
Cor (ng/L)	0.296	0.007
NE (ng/L)	0.296	0.007
SOD (U/mL)	–0.399	<0.001

Oxidative stress: In the acute and chronic phases, oxidative stress levels were measured in all patients. Early in the morning of the test day, 5 mL of fasting blood was drawn, and the supernatant was centrifuged after static centrifugation, and then the levels of human cortisol (Cor) and norepinephrine (NE) were measured by ELISA enzyme immunoassay. The enzyme activity of superoxide dismutase (SOD) was measured by using a BioSpectrometer spectrophotometer from Eppendorf, Germany.

Cognitive function: the patients' cognitive function was evaluated by using the Mini-Mental State Examination (MMSE), which includes subscores that assess orientation, memory, recall, language, attention, and calculation. The MMSE has a total possible score of 30 points, and a score <27 suggests cognitive impairment in the patient [7]. The patients were also classified according to their literacy level to determine whether they suffered from cognitive impairment: high school and above <27 points, middle school ≤24 points, elementary school ≤20 points, and illiteracy ≤17 points.

Statistical Analysis

SPSS 21.0 software (IBM, Armonk, NY, USA) was used for data processing and analysis. Continuous variables were expressed as ($\bar{x} \pm$ sem) and the paired samples *t* test was used to test differences between groups. Categorical variables were expressed as % and associations between variables were analyzed using the χ^2-test. Spearman's correlation was used to test associations between the inflammatory and oxidative stress measures and MMSE scores, and logistic regression was used to test relevant factors of patients' concurrent cognitive impairment. The receiver operating characteristic (ROC) curve was used to assess the value of inflammatory and oxidative stress measures for prediction of concurrent cognitive impairment in the acute and chronic phases. p values < 0.05 were considered statistically significant.

Results

Comparison of the Levels of Inflammatory Factors and Oxidative Stress in Patients at Different Times

The patients had higher levels of IL-6, IL-10, TNF-α, CRP, Cor, and NE, and lower levels of SOD, in the acute phase compared to the chronic phase, and the differences were statistically significant ($p < 0.05$, Table 1).

Comparison of Patients' Level of Cognitive Function over Time

The patients' acute phase MMSE score was (28.74 ± 0.73) and their chronic phase MMSE score was (26.78 ± 1.07). Thus, MMSE scores in the acute phase were higher than MMSE scores in the chronic phase, and the difference was statistically significant ($t = 13.702$, $p < 0.05$). A total of 50 cases (60.98%) of cognitive impairment were identified and all of them were in the chronic stage.

Table 3. Single-factor analysis according to concurrent cognitive impairment.

Indicators	Cognitive impairment group (n = 50)	Cognitively normal group (n = 32)	t/χ^2	p
Genders				
Male	27 (54.00)	16 (50.00)	0.125	0.723
Female	23 (46.00)	16 (50.00)		
Age (years)	47.90 ± 3.49	45.78 ± 3.09	2.803	0.006
Educational attainment				
High school and above	20 (40.00)	21 (65.63)	5.125	0.024
Less than high school	30 (60.00)	11 (34.38)		
Causes of injury				
Fall from a height	15 (30.00)	10 (31.25)	0.349	0.840
Wreck	32 (64.00)	21 (65.63)		
Other	3 (6.00)	1 (3.13)		
Location of injury				
Frontal lobe	32 (64.00)	12 (37.50)	5.510	0.019
Other	18 (36.00)	20 (62.50)		
Surgical procedures				
Craniectomy	21 (42.00)	13 (40.63)	0.015	0.902
Cranial repair	29 (58.00)	19 (59.38)		
Smoking history				
Yes	18 (36.00)	10 (31.25)	0.196	0.658
No	32 (64.00)	22 (68.75)		
Drinking history				
Yes	15 (30.00)	8 (25.00)	0.242	0.623
No	35 (70.00)	24 (75.00)		
Acute phase				
IL-6 (ng/L)	42.44 ± 7.00	43.52 ± 6.36	0.706	0.482
IL-10 (ng/L)	36.61 ± 5.47	36.48 ± 5.58	0.104	0.917
TNF-α (ng/L)	36.93 ± 10.18	37.23 ± 10.18	0.130	0.897
CRP (mg/L)	34.73 ± 8.81	34.48 ± 7.50	0.133	0.895
Cor (ng/L)	181.35 ± 13.57	182.34 ± 12.80	0.329	0.743
NE (ng/L)	296.73 ± 22.60	296.07 ± 22.18	0.130	0.897
SOD (U/mL)	3.09 ± 0.25	3.14 ± 0.28	0.843	0.402
Chronic phase				
IL-6 (ng/L)	22.73 ± 4.60	19.28 ± 5.32	3.115	0.003
IL-10 (ng/L)	18.28 ± 3.46	15.59 ± 3.51	3.415	0.001
TNF-α (ng/L)	30.98 ± 5.60	26.52 ± 6.45	3.315	0.001
CRP (mg/L)	26.97 ± 4.43	23.77 ± 5.78	2.829	0.006
Cor (ng/L)	144.96 ± 9.73	138.27 ± 12.36	2.730	0.008
NE (ng/L)	236.26 ± 14.99	226.27 ± 18.55	2.681	0.009
SOD (U/mL)	3.37 ± 0.34	3.66 ± 0.34	3.768	<0.001

Analysis of the Correlation between the Levels of Inflammatory Factors and Oxidative Stress and Cognitive Impairment

Spearman's correlation analysis revealed that the levels of IL-6, IL-10, TNF-α, CRP, Cor, and NE in the chronic phase were positively correlated with concurrent cognitive impairment, and the levels of SOD were negatively correlated with concurrent cognitive impairment ($p < 0.05$, Table 2).

Single-Factor Analysis According to Concurrent Cognitive Impairment

Patients were divided into a cognitively impaired group (n = 50) and a cognitively normal group (n = 32) according to their cognitive function. In the chronic phase, the cognitively impaired group had significantly higher levels of IL-6, IL-10, TNF-α, CRP, Cor, and NE, and a lower level of SOD, compared with the cognitively normal group. The percentages of below high school and frontal lobe damage

Table 4. Multifactorial analysis of factors affecting patients with concurrent cognitive impairment.

Influencing factors	β value	SE value	Wald value	p value	OR value	95% CI
Educational attainment	2.021	0.873	5.359	0.021	7.547	(1.363, 41.777)
Location of injury	2.125	0.907	5.484	0.019	8.373	(1.414, 49.579)
Chronic phase IL-6	0.342	0.124	7.592	0.006	1.408	(1.104, 1.796)
Chronic phase IL-10	0.486	0.162	8.967	0.003	1.626	(1.183, 2.234)
Chronic phase TNF-α	0.179	0.074	5.817	0.016	1.196	(1.034, 1.382)
Chronic phase CRP	0.352	0.128	7.617	0.006	1.422	(1.107, 1.826)
Chronic phase SOD	–2.783	1.397	3.965	0.046	0.062	(0.004, 0.957)
Constants	–21.628	8.852	5.970	0.015		

SE, standard error; OR, odds ratio; CI, confidence interval.

Table 5. Analysis of the predictive value of each differential indicator for patients with concurrent cognitive impairment.

Projects	AUC	Standard error	p	95% CI	Yoden index	Truncation value	Sensitivity	Specificity
Educational attainment	0.628	0.063	0.051	(0.504, 0.752)	0.256	-	0.600	0.656
Location of injury	0.633	0.063	0.044	(0.508, 0.757)	0.265	-	0.6400	0.625
Chronic phase IL-6	0.678	0.062	0.007	(0.556, 0.799)	0.385	20.155	0.760	0.625
Chronic phase IL-10	0.706	0.061	0.002	(0.587, 0.826)	0.501	17.040	0.720	0.781
Chronic phase TNF-α	0.709	0.063	0.001	(0.585, 0.832)	0.487	27.340	0.800	0.687
Chronic phase CRP	0.675	0.066	0.008	(0.546, 0.804)	0.450	25.515	0.700	0.750
Chronic phase SOD	0.736	0.059	0.000	(0.620, 0.853)	0.532	3.495	0.720	0.812
United	0.949	0.029	0.000	(0.891, 1.000)	0.824	-	0.980	0.844

AUC, area under the curve.

were higher in the cognitively impaired group compared with the cognitively normal group, and the differences were statistically significant ($p < 0.05$, Table 3).

Multifactorial Analysis of Factors Affecting Patients with Concurrent Cognitive Impairment

For the logistic regression analysis, whether the patients had concurrent cognitive impairment was included as the dependent variable, and age, literacy, site of injury, and levels of inflammatory factors and oxidative stress indicators in the chronic phase were included as covariates. Variables were coded as follows: cognitive impairment was 1, uncomplicated was 0; below high school was 1, high school and above was 0; frontal lobe injury was 1, and uninjured frontal lobe was 0. The analysis showed that below high school, frontal lobe injury, higher levels of IL-6, IL-10, TNF-α, and CRP, and a lower level of SOD were all relevant factors affecting the patients' concurrent cognitive impairment (Table 4).

Analysis of the Predictive Value of Each Differential Indicator for Patients with Concurrent Cognitive Impairment

As shown by the ROC curve, the area under the curve (AUC) for the combination of indicators was 0.949, sensitivity was 0.980, and specificity was 0.844 (Table 5, Fig. 1).

Discussion

Craniocerebral injury is caused by external force and impairs the normal functioning of the brain. According to the patient's symptoms, the injury can be classified as mild, moderate, or severe, and can cause the emergence of headache, dizziness, impaired consciousness, speech dysfunction, motor dysfunction, emotional changes, and other symptoms. At present, the Glasgow Coma Scale (GCS) score is commonly used to evaluate the degree of patient's symptoms; a GCS score $\leq$8 points suggests severe craniocerebral injury [8,9]. Patients with severe craniocerebral injuries have more serious damage to brain tissues, with a higher risk of neurological damage, which can affect patients' memory, cognition, and behavioral abilities, and can lead to complications such as cognitive impairment [10].

Inflammation plays an important role in craniocerebral injuries. Talaat *et al.* [11] showed a correlation between higher levels of inflammation and concurrent cognitive impairment. High levels of inflammation may negatively affect the normal functioning of the brain, leading to cognitive impairment [12]. Therefore, in patients with severe craniocerebral injuries, we need to pay close attention to changes in the level of inflammation and target inflammation appropriately to reduce the risk of complications such as cognitive impairment. In the present study, it was found that in the acute phase of severe craniocerebral

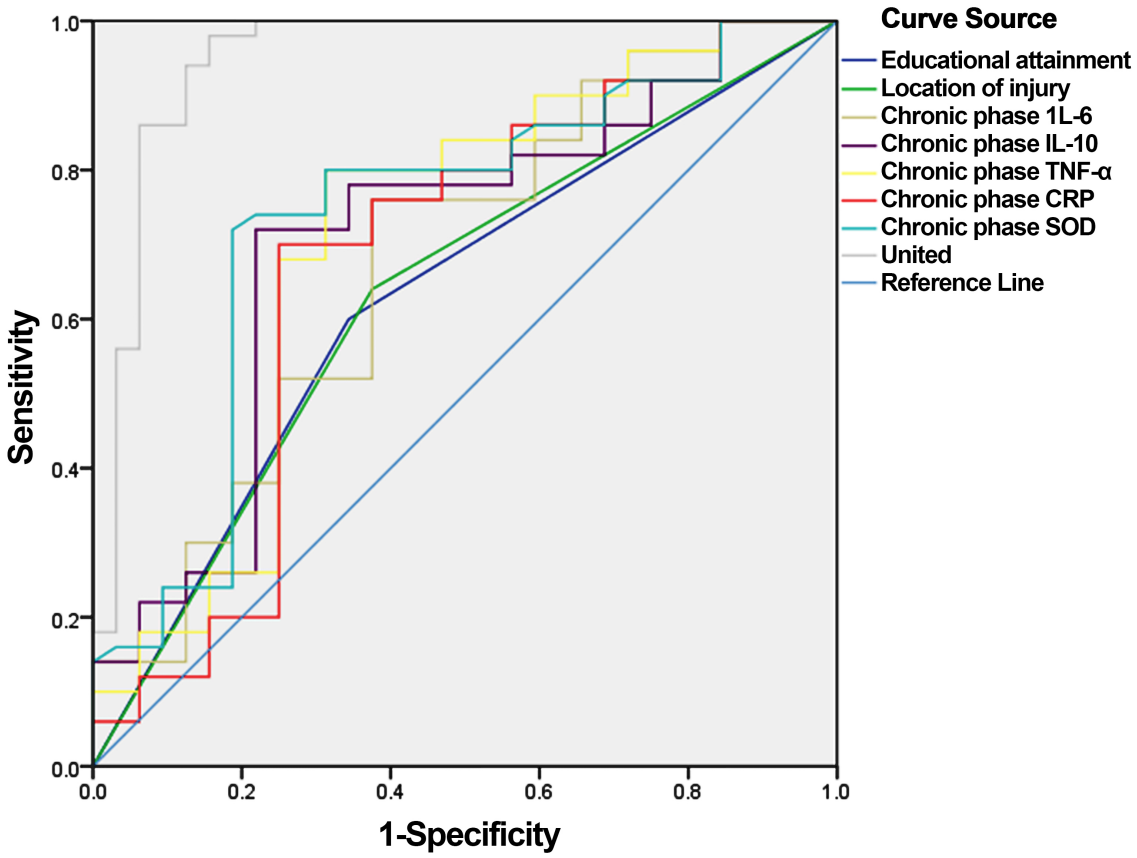

Fig. 1. Receiver operating characteristic (ROC) graph.

injury, the levels of inflammatory factors such as IL-6, IL-10, TNF-α, and CRP were at high levels in patients. Sulimai *et al.* [13] also showed that during the acute phase of brain injury, the body has higher levels of inflammatory factors, and that higher levels of inflammation correlate with the patient's concurrent symptoms such as memory loss. In addition, the present study revealed that when the patients transitioned from the acute to the chronic phase, the levels of all inflammatory factors, although reduced, were still at a high level, indicating that the inflammation persisted for a long period of time. Inflammation is the body's self-protective response to damage, but an excessive inflammatory response may cause more damage to brain tissue [14]. The reason may be that patients with severe craniocerebral injury have more serious brain tissue damage, and the body gradually recovers with the development of time, but the limited ability of the brain tissue to repair severe structural trauma will result in the long-term presence of inflammation, and the overexpression of inflammatory factors may lead to sustained damage to the nervous system and result in the slow recovery of cognitive function or imbalance.

On the other hand, craniocerebral injuries can cause a complex neurometabolic cascade, including neuroinflammation and oxidative stress, among which oxidative stress can lead to mitochondrial dysfunction and secondary neuronal damage, which can negatively affect the recovery of cognitive function in patients [15]. In the present study, it was found that when the patients transitioned from the acute to the chronic stage, the levels of Cor and NE were decreased and the levels of SOD were increased, indicating that when craniocerebral injury occurs, it will contribute to an increase in the degree of oxidative stress in the body. It has been reported in mice that SOD activity was up-regulated in order to alleviate traumatic brain injury caused by re-induced hypoxia [16]. However, Albanawany *et al.* [17] showed that SOD activity was lower in the chronic phase than in the acute phase, contradicting the results of the present study. The reason for these results may be that the SOD level in the chronic phase was higher than that in the acute phase, indicating that the SOD level was continuously up-regulated, suggesting that the level of oxidative stress gradually increased, but unlike the enhancement of the SOD activity in the acute phase, the overexpression of SOD in the chronic phase may be a compensatory mech-

anism, which may be related to the activation of the peripheral macrophage and the disruption of the blood-brain barrier [18]. It was also found that MMSE scores were positively correlated with IL-6, IL-10, TNF-α, CRP, and NE levels and negatively correlated with SOD levels in both acute and chronic phases. It has been suggested that the levels of inflammatory factors and oxidative stress are closely related to patients' cognitive function, and when the levels of inflammatory factors and oxidative stress are too high, it will be detrimental to the recovery of cognitive function. Shimoura *et al*. [19] likewise suggests that high levels of inflammatory factors and oxidative stress will lead to neuroinflammation and cerebrovascular damage, with consequent effects on cognitive function.

In the present study, regression analysis revealed that patients with higher levels of inflammatory factors and oxidative stress in the chronic phase, lower literacy, and frontal lobe damage were more likely to have concurrent cognitive impairment. The higher level of inflammatory factors in the chronic phase suggests a higher level of inflammation in the body, and the sustained high level of inflammatory response will cause damage to the nervous system, which will have an impact on cognitive function, Bellocchi *et al*. [20] also found that a high level of inflammatory response will lead to an elevated risk of cognitive impairment in patients with concurrent cognitive deficits. The lower level of SOD in the chronic phase implies that the level of oxidative stress decreases, but the patients with severe brain tissue damage may suffer from hypoxia, which may exacerbate the damage to brain tissue and ultimately affect cognitive function. Patients with lower levels of literacy may be in poorer shape with respect to vocabulary integration, memory, and concepts, which may result in a higher incidence of cognitive impairment. The frontal lobe is one of the key areas of the brain responsible for higher cognitive functions, including attention and memory, decision-making and judgment, emotional and behavioral control, etc. Therefore, when the frontal lobe is damaged, it leads to an increased risk of cognitive impairment. In addition, ROC analysis revealed that the combined effect of all the indices was better, so these indices can be used to assist in predicting the risk level of the patients' concurrent cognitive impairment in the clinic.

The current study still has several limitations. There was no sample size calculation for this study, and subsequent studies will seek to identify more suitable studies to use as sample references. The small sample size included in this study may lead to bias in the results obtained, and the next study will employ a larger sample. The information collected in this study did not fully reflect the effect of baseline differences on patients' concurrent cognitive impairment. To increase the reliability of the results, subsequent studies will look for similar references, in order to include additional influencing factors.

Conclusions

The incidence of cognitive impairment is higher in patients with severe craniocerebral injury, and the levels of inflammatory factors and oxidative stress, which are not conducive to recovery, are higher in patients in the acute stage. This study revealed that the risk of concurrent cognitive impairment is higher in patients with a lower level of literacy, frontal lobe injury, and high levels of inflammatory factors and oxidative stress in the chronic stage; thus, these indicators have a significant predictive effect on the prognosis of the patients.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

LMY and YDC designed the research study. LMY and YH performed the research and analyzed the data. All authors contributed to the drafting or important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted with the approval and consent of the Longyou County People's Hospital ethics committee (No.202211). Patients and their families signed informed consent. All procedures of this study were conducted in accordance with relevant ethical standards such as the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Pease M, Arefan D, Barber J, Yuh E, Puccio A, Hochberger K, *et al*. Outcome Prediction in Patients with Severe Traumatic Brain Injury Using Deep Learning from Head CT Scans. Radiology. 2022; 304: 385–394.

[2] Gao Y, Liao LP, Chen P, Wang K, Huang C, Chen Y, *et al*. Application effect for a care bundle in optimizing nursing of patients with severe craniocerebral injury. World Journal of Clinical Cases. 2021; 9: 11265–11275.

[3] Brett BL, Gardner RC, Godbout J, Dams-O'Connor K, Keene CD. Traumatic Brain Injury and Risk of Neurodegenerative Disorder. Biological Psychiatry. 2022; 91: 498–507.

[4] Jamjoom AAB, Rhodes J, Andrews PJD, Grant SGN. The synapse in traumatic brain injury. Brain: a Journal of Neurology. 2021; 144: 18–31.

[5] Witcher KG, Bray CE, Chunchai T, Zhao F, O'Neil SM, Gordillo AJ, *et al*. Traumatic Brain Injury Causes Chronic Cortical Inflammation and Neuronal Dysfunction Mediated by Microglia. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2021; 41: 1597–1616.

[6] Herz J, Bendix I, Felderhoff-Müser U. Peripheral immune cells and perinatal brain injury: a double-edged sword? Pediatric Research. 2022; 91: 392–403.

[7] Zhang J, Wang X, Zhang Q, Wang Z, Zhu S. Application effects of remimazolam and propofol on elderly patients undergoing hip replacement. BMC Anesthesiology. 2022; 22: 118.

[8] Wang Y, Huang C, Tian R, Yang X. Target temperature management and therapeutic hypothermia in sever neuroprotection for traumatic brain injury: Clinic value and effect on oxidative stress. Medicine. 2023; 102: e32921.

[9] King JA, McCrea MA, Nelson LD. Frequency of Primary Neck Pain in Mild Traumatic Brain Injury/Concussion Patients. Archives of Physical Medicine and Rehabilitation. 2020; 101: 89–94.

[10] Zhang HY, Tian Y, Shi HY, Cai Y, Xu Y. The critical role of the endolysosomal system in cerebral ischemia. Neural Regeneration Research. 2023; 18: 983–990.

[11] Talaat F, Abdelatty S, Ragaie C, Dahshan A. Chitinase-3-like 1-protein in CSF: a novel biomarker for progression in patients with multiple sclerosis. Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2023; 44: 3243–3252.

[12] Jin M, Cai SQ. Mechanisms Underlying Brain Aging Under Normal and Pathological Conditions. Neuroscience Bulletin. 2023; 39: 303–314.

[13] Sulimai N, Lominadze D. Fibrinogen and Neuroinflammation During Traumatic Brain Injury. Molecular Neurobiology. 2020; 57: 4692–4703.

[14] Kim H, Han S, Song K, Lee MY, Park B, Ha IJ, *et al*. Ethyl Acetate Fractions of *Papaver rhoeas* L. and *Papaver nudicaule* L. Exert Antioxidant and Anti-Inflammatory Activities. Antioxidants (Basel, Switzerland). 2021; 10: 1895.

[15] Chojdak-Łukasiewicz J, Bizoń A, Waliszewska-Prosół M, Piwowar A, Budrewicz S, Pokryszko-Dragan A. Role of Sirtuins in Physiology and Diseases of the Central Nervous System. Biomedicines. 2022; 10: 2434.

[16] Zhang W, Hong J, Zhang H, Zheng W, Yang Y. Astrocyte-derived exosomes protect hippocampal neurons after traumatic brain injury by suppressing mitochondrial oxidative stress and apoptosis. Aging. 2021; 13: 21642–21658.

[17] Albanawany NM, Samy DM, Zahran N, El-Moslemany RM, Elsawy SM, Abou Nazel MW. Histopathological, physiological and biochemical assessment of resveratrol nanocapsules efficacy in bleomycin-induced acute and chronic lung injury in rats. Drug Delivery. 2022; 29: 2592–2608.

[18] Ramírez-Mendoza AA, Ramírez-Herrera MA, Cortez-Álvarez CR, Nery-Flores SD, Tejeda-Martínez AR, Romero-Prado MMDJ, *et al*. Curcumin Modifies the Activity of Plasmatic Antioxidant Enzymes and the Hippocampal Oxidative Profile in Rats upon Acute and Chronic Exposure to Ozone. Molecules (Basel, Switzerland). 2022; 27: 4531.

[19] Shimoura CG, Wallace K, Mathis KW. Editorial: Renal injury and the brain. Frontiers in Medicine. 2023; 9: 1100487.

[20] Bellocchi C, Carandina A, Montinaro B, Targetti E, Furlan L, Rodrigues GD, *et al*. The Interplay between Autonomic Nervous System and Inflammation across Systemic Autoimmune Diseases. International Journal of Molecular Sciences. 2022; 23: 2449.