



# Levels of S100 calcium binding protein B (S100B), neuron-specific enolase (NSE), and cyclophilin A (CypA) in the serum of patients with severe craniocerebral injury and multiple injuries combined with delirium transferred from the ICU and their prognostic value

Yang Gao<sup>1,2#</sup>, Jun Duan<sup>2,3#</sup>, Hong Ji<sup>2,4</sup>, Weifeng Lu<sup>2,5</sup>

<sup>1</sup>Department of general practice center, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China; <sup>2</sup>Chinese Academy of Sciences Sichuan Translational Medicine Research Hospital, Chengdu, China; <sup>3</sup>Department of Geriatrics, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China; <sup>4</sup>Department of geriatric medicine, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China; <sup>5</sup>Department of anesthesia operation center, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China

*Contributions:* (I) Conception and design: Y Gao, J Duan; (II) Administrative support: H Ji, W Lu; (III) Provision of study materials or patients: Y Gao, J Duan; (IV) Collection and assembly of data: Y Gao, J Duan; (V) Data analysis and interpretation: Y Gao, J Duan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

<sup>#</sup>These authors contributed equally to this work.

*Correspondence to:* Weifeng Lu. Department of Anesthesia Operation Center, No.32 West Section 2, First Ring Road, Chengdu 610072, China. Email: fengjie667@163.com; Hong Ji. Department of Geriatric Medicine, No.32 West Section 2, First Ring Road, Chengdu 610072, China. Email: ekkjxstmimwh30@sina.com.

**Background:** To analyze the levels of S100 calcium binding protein B (S100B), neuron-specific enolase (NSE), and cyclophilin A (CypA) in the serum of patients with severe craniocerebral injury combined with delirium and multiple injuries transferred from the intensive care unit (ICU), and their prognostic value.

**Methods:** The data of 98 patients with severe craniocerebral injury combined with delirium and multiple injuries admitted to our hospital from January 2018 to May 2019 were retrospectively analyzed as the study group. The differences in serum S100B, NSE, and CypA levels in each group were compared, and the deaths of the study group during follow-up were counted.

**Results:** The levels of S100B, NSE, and CypA in the study group were higher than those in the control group ( $P < 0.05$ ). The mortality rate of the 98 patients with severe craniocerebral injury combined with delirium and multiple injuries transferred from the ICU was 37.76%. Furthermore, the levels of S100B, NSE, and CypA in the death group were higher than those in the survival group ( $P < 0.05$ ). Glasgow Coma Score (GCS) score  $\leq 5$  points, Injury Severity Score (ISS) score  $> 25$  points, multiple organ dysfunction syndrome, and increased levels of S100B, NSE, and CypA were independent risk factors that affected the prognosis of patients with severe craniocerebral injury combined with delirium and multiple injuries transferred from the ICU ( $P < 0.05$ ). The average survival times of the high S100B level group, the high NSE level group, and the high CypA level group were shorter than those of the low-level groups ( $P < 0.05$ ).

**Conclusions:** The levels of S100B, NSE, and CypA in serum were closely related to the prognosis of patients with severe craniocerebral injury combined with delirium and multiple injuries transferred from the ICU. They can be used as molecular markers for predicting the prognosis of patients, and may serve as potential targets for treatment.

**Keywords:** Severe craniocerebral injury-based multiple injuries; delirium; serum S100 calcium binding protein B (serum S100B); neuron-specific enolase (NSE); cyclophilin A (CypA)

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## Introduction

Multiple injuries refer to the same injury factor causing 2 or more serious injuries to the human body at the same time or one after another. In recent years, the incidence of multiple injuries has increased year by year. Among them, severe head injuries combined with multiple injuries account for 10% to 20% (1). Delirium is a relatively common clinical acute mental syndrome with rapid clinical development. During the period of admission to the intensive care unit (ICU) for severe head injury, patients with multiple injuries are more likely to experience delirium than ordinary patients, under the combined influence of environmental factors, psychological factors, therapeutic measures, and disease (2,3). With the development of intensive care medicine, the initial treatment success rate of patients with severe head injuries and delirium combined with multiple injuries has been greatly improved. In recent years, the prognosis of patients transferred from the ICU has become the focus of attention (4,5).

S100 calcium binding protein B (S100B) is a specific index that can predict the severity of cerebrovascular damage, guide clinical treatment, and judge prognosis. Neuron-specific enolase (NSE) is a specific marker of neuronal damage. The value of both markers in craniocerebral injuries has been recognized (6,7). Cyclophilin A (CypA) is an important factor involved in immune regulation, inflammatory responses, and cell growth, amongst other processes, and its role in the prognostic evaluation of critically ill patients has attracted attention (8). Increased serum CypA concentrations reflect trauma severity and unfavorable outcomes after head trauma, making CypA a potential biomarker for the prognostic prediction of traumatic brain injury (TBI) (9). This study analyzed the serum levels of S100B, NSE, and CypA in patients transferred from the ICU with severe head injury and delirium, aiming to reveal the value of these 3 markers for the prediction of prognosis. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/apm-21-424>).

## Methods

### *Patient information*

In this retrospective analysis, 98 patients with combined severe craniocerebral injury and delirium from January 2018 to May 2019 at our hospital were used as the research group. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China (No. 20171208). All patients agreed to participate in this study and signed an informed consent form. The inclusion criteria were as follows: (I) a clear history of head injury; (II) Glasgow Coma Score (GCS) (10)  $\leq 8$  points; (III) head CT examination after admission showed brain contusion or brain injury contusion and laceration, obvious intracerebral hematoma and/or brain herniation, brain stem injury, and/or multiple skull fractures; (IV) Injury Severity Score (ISS) (11)  $\geq 16$  points; (V) the clinical data was complete with no missing information. The exclusion criteria were as follows: (I) patients had concomitant serious organic diseases of the heart, liver, and kidney, or other tumors; (II) occurrence of heart, cerebral stroke, or brain trauma within the 6 months before enrollment; (III) use of anticoagulants or anti-platelet drugs within the 3 months before enrollment; (IV) had blood system diseases, such as combined leukemia, idiopathic thrombocytopenic purpura, or hemophilia, amongst others; (V) had acute and chronic infections within the 1 month before enrollment.

There were 53 males and 45 females in the research group, aged from 18 to 70 years old, with an average age of  $39.64 \pm 8.57$  years old. Among them, 46 were traffic accidents, 22 were bruises, 20 were fall injuries, and the other 10 were. There were 76 cases of closed head injury and 22 cases of open head injury. The control group consisted of 90 patients who had a physical examination during the same period in our hospital. There were no statistically significant differences in age and gender compared with the research group, and they were comparable ( $P > 0.05$ ).

**Table 1** Comparison of S100B, NSE, and CypA levels between the research group and the control group

Group	S100B (pg/mL)	NSE (μg/L)	CypA (ng/mL)
Research group (n=98)	624.51±120.36	39.62±12.74	99.63±30.41
Control group (n=90)	36.74±10.59	10.50±2.31	13.54±3.48
t	46.155	21.360	26.691
P value	<0.001	<0.001	<0.001

S100B, S100 calcium binding protein B; NSE, neuron-specific enolase; CypA, cyclophilin A.

### Research methods

After admission, the patients in the study group were diagnosed based on the results of medical history, physical examination, laboratory examination, and special examinations (such as B-ultrasound, chest X-ray, CT, etc.), and the injury was fully estimated. The combined injuries were then treated in the order of chest, abdomen, brain, and limbs. That is, for patients with thoracic organ damage and hemorrhagic shock, controlling the bleeding and correcting dyspnea were the first tasks, followed by strengthening the treatment and support for the damage of vital organs, such as maintaining airway patency, anti-shock therapy, handling blood pneumothorax. If there were multiple organ injuries in the abdominal cavity, the first task was to control bleeding and repair the perforated organ as soon as possible, and remove the intracranial hematoma at the same time or later. Both postoperative patients and non-surgical patients received conventional trauma surgery interventions, dehydrating agents, brain protective agents, prevention of infection, enteral nutrition support, or rehabilitation treatment as needed.

The clinical data of all the study subjects were collected, and the serum levels of S100B, NSE, and CypA were compared between the research group (within 12 hours before being transferred from the ICU) and the control group. Subsequently, 98 patients who were transferred out of the ICU with severe head injury and delirium were followed up for a period of 30 days, and their deaths during the follow-up period were counted. The related factors that affected the prognosis of patients transferred from the ICU with severe head injury and delirium were analyzed by unconditional univariate and multivariate logistic regression

models. Kaplan-Meier survival curves were generated to study the effects of serum S100B, NSE, and CypA levels on the prognosis of patients.

### Determination of S100B, NSE, and CypA levels

Venous blood (cubital vein) was collected in a heparin anticoagulation tube and centrifuged (1,500 r/min, 10 min), and the supernatant was stored in a refrigerator at -20 °C. The serum levels of NSE, S100B, and CypA were determined by enzyme-linked immunosorbent assay (ELISA). The Elecsys2010 electroluminescence automatic immunoassay instrument (Roche, Japan) was used for detection, and the NSE kit was produced by Roche, Germany. The serum levels of S100B and CypA were detected using the Bio-Rad Coda automatic enzyme immunoassay instrument (Bio-Rad, Hercules, CA, USA) according to the kit instructions.

### Statistical analysis

The data in this study were statistically analyzed by SPSS22.0 software, the count data were expressed as n (%), and an independent sample t-test was used. Multivariate logistic regression analysis was used to analyze the risk factors affecting the prognosis and survival of patients transferred from the ICU with severe head injury and delirium. Kaplan-Meier survival curves were used to assess the predictive value of S100B, NSE, and CypA for the prognosis of patients. Differences were statistically significant when  $P < 0.05$ .

## Results

### Comparison of S100B, NSE, and CypA levels between the research group and the control group

The expression levels of S100B, NSE, and CypA in the research group were higher than those in the control group ( $P < 0.05$ ), as shown in *Table 1*.

### Prognosis and survival of the 98 patients

By the end of the follow-up, out of the 98 patients who were transferred out of the ICU with severe head injury and delirium, 37 patients died, 61 patients survived, and the mortality rate was 37.76%.

### Comparison of S100B, NSE, and CypA levels between the survival group and death group

The expression levels of S100B, NSE, and CypA in the death group were higher than those in the survival group ( $P < 0.05$ ), as shown in *Table 2*.

### Multivariate analysis

GCS score  $\leq 5$  points, ISS score  $> 25$  points, multiple organ

**Table 2** Comparison of S100B, NSE, and CypA levels between the survival group and death group

Group	S100B (pg/mL)	NSE ( $\mu\text{g/L}$ )	CypA (ng/mL)
Death group (n=37)	706.41 $\pm$ 50.74	49.86 $\pm$ 3.67	110.80 $\pm$ 10.59
Survival group (n=61)	563.05 $\pm$ 52.95	20.71 $\pm$ 3.85	85.69 $\pm$ 12.03
t	13.197	36.974	10.468
P value	<0.001	<0.001	<0.001

S100B, S100 calcium binding protein B; NSE, neuron-specific enolase; CypA, cyclophilin A; P value, Probability

dysfunction syndrome, and abnormally elevated levels of S100B, NSE, and CypA were independent risk factors for the prognosis of patients with multiple injuries combined with delirium who were transferred out of the ICU with severe head injury ( $P < 0.05$ ), as shown in *Table 3*.

### The relationship between S100B, NSE, and CypA levels on the prognosis and survival of patients

As shown in *Figure 1*, Kaplan-Meier survival curves were significantly different between the different expression levels of S100B, NSE, and CypA. The average survival time of the high S100B level group was shorter than that of the low-level group ( $P < 0.05$ ). The average survival time of the high NSE level group was shorter than that of the low-level group ( $P < 0.05$ ). The average survival time of the high CypA level group was shorter than that of the low-level group ( $P < 0.05$ ).

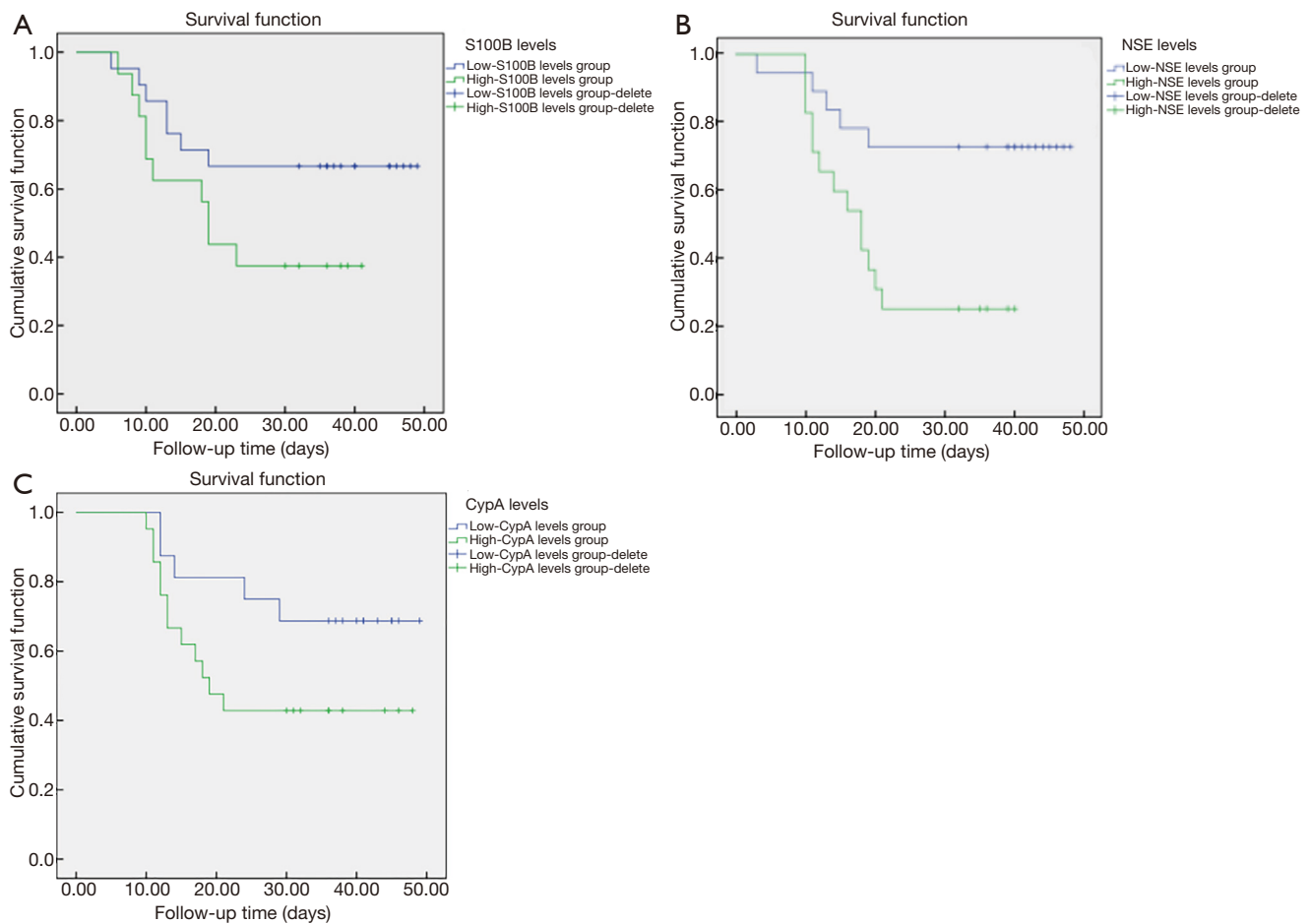
### Discussion

Multiple injuries combined with craniocerebral injury are harmful, and are one of the most significant causes

**Table 3** Multivariate analysis of factors affecting the prognosis of patients transferred out of the ICU with severe head injury and delirium combined with multiple injuries

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age (<60 vs. $\geq 60$ years)	2.342	1.805–3.039	0.025	1.642	0.814–3.312	–
Gender (male vs. female)	2.759	0.917–8.302	0.162	–	–	–
GCS score ( $> 5$ vs. $\leq 5$ points)	2.333	1.611–3.379	0.006	4.669	1.182–18.448	<0.001
ISS score (16–25 vs. $> 25$ points)	2.883	1.991–4.176	0.003	2.524	1.543–4.129	<0.001
High blood sugar (yes vs. no)	4.531	3.129–6.563	0.007	2.396	0.531–10.818	0.094
Shock (yes vs. no)	2.601	2.04–3.376	0.019	2.883	0.422–19.684	
Multiple organ dysfunction syndrome (yes vs. no)	2.396	1.655–3.471	<0.001	2.433	1.487–3.979	<0.001
Systemic inflammatory response syndrome (yes vs. no)	2.604	1.798–3.771	<0.001	2.649	0.670–10.464	0.130
ICU treatment time (<12 vs. $\geq 12$ d)	2.268	1.751–2.938	<0.001	2.408	0.610–9.516	0.266
Mechanical ventilation (yes vs. no)	2.710	2.092–3.510	<0.001	2.098	0.531–8.289	0.104
S100B levels (elevated vs. normal)	2.349	1.914–3.043	<0.001	2.625	1.605–4.293	<0.001
NSE levels (elevated vs. normal)	4.116	1.368–12.385	<0.001	2.591	1.584–4.237	<0.001
CypA levels (elevated vs. normal)	2.787	2.181–3.561	<0.001	2.875	1.758–4.702	<0.001

ICU, intensive care unit; GCS, Glasgow Coma Score; ISS, Injury Severity Score; S100B, S100 calcium binding protein B; NSE, neuron-specific enolase; CypA, cyclophilin A. OR, odds ratio; CI, Confidence interval; P value, probability



**Figure 1** The relationship between S100B, NSE, and CypA levels on the prognosis and survival of patients. S100B, S100 calcium binding protein B; NSE, neuron-specific enolase; CypA, cyclophilin A.

of disability and death (12). Delirium refers to a group of symptoms of organic mental disorders, including disturbances in consciousness, significant excitement, restlessness, and disturbance in perception. Clinical practice has found that patients with severe head injury are prone to diffuse brain changes after delirium (13,14). The progress of basic research and clinical research in recent years has shown that interventions for such patients are extremely important. Dynamic observation and accurate and effective treatment must be adopted to reduce the mortality rate (15,16).

The S100B protein is an acidic calcium-binding protein, which is mainly found in astrocytes and oligodendrocytes of the central nervous system, and Schwann cells of the peripheral nervous system. It is currently believed that due to the integrity of brain cells and the blood-brain barrier in normal people, the content of S100B in cerebrospinal fluid is extremely low (17). Brain injury can be accompanied

by mechanical brain cell destruction and blood-brain barrier damage, resulting in S100B being released outside the cell and entering the blood circulation (18-20). However, the mechanism of S100B as a marker of damage or in neuroprotection related to the pathophysiology of craniocerebral injury is still unclear. Therefore, this study analyzed the expression of the S100B protein in patients who were transferred from the ICU with severe craniocerebral injury and delirium. The levels of S100B have been shown to increase after craniocerebral injury and then decrease quickly, indicating an improvement in the patients' condition, then levels increase again or continue to increase, indicating that secondary injury or primary injury was aggravated (21). Furthermore, after 2 weeks of IFN- $\alpha$  therapy, S100B concentrations were shown to be higher in individuals with increased symptoms of depression, but the difference was not statistically significant (22). The variation

in S100B concentration was mainly dependent on the degree of blood-brain barrier destruction and the severity and scope of brain injury. In this study, Kaplan-Meier survival curves demonstrated the relationship between S100B expression levels and patient prognosis, and the results showed that the survival time of the high expression group was shorter than that of the low expression group. It further showed that determining S100B levels could reflect the severity of head injury and predict the progression of the disease.

NSE belongs to the  $\gamma\gamma$  subtype of the 5 enolase isoenzymes  $\alpha\alpha$ ,  $\beta\beta$ ,  $\gamma\gamma$ ,  $\alpha\beta$ , and  $\alpha\gamma$  that have been discovered. It is ubiquitous in the glycolytic metabolism of organisms, and can catalyze the conversion of  $\alpha$ -glycerol phosphate to phosphoenolpyruvate (23,24). NSE has been proven to provide quantitative measurement of brain injury and/or ameliorate the diagnosis and outcome evaluation of ischemic stroke, cerebral hemorrhage, epilepsy, traumatic brain injury and coma patients after cardiopulmonary resuscitation (25). In another study, the change in NSE serum levels over time was different in patients with primary cortical contusion, diffuse axonal injury, and cerebral edema without local mass effect, suggesting that dynamic monitoring of NSE levels may help reflect the different physiological and pathological conditions after head injury (26). In the dexmedetomidine group, the median values of brain-derived neurotrophic factor (BDNF), NSE and S100B were significantly lower on the day of the diagnosis of delirium and the third day after the diagnosis of delirium. The incidence of irritation in the dexmedetomidine group was significantly lower than that in the normal group (27). The results of this study showed that the NSE level of the research group was higher than that of control group, and the survival time of the NSE high expression group was much lower than that of the low expression group. These results suggested that the determination of serum NSE levels could help evaluate the prognosis of patients with severe head injuries combined with delirium and multiple injuries.

CypA is the earliest discovered and most widely studied cyclophilin, which has a variety of biological functions. Recent studies have shown that CypA is also an intracellular receptor for cyclosporin, which can modulate cyclosporin to exert immunosuppressive effects, thereby regulating the body's immune function and inflammatory response (28,29). Several studies have implicated CypA as a mediator of the ApoE4 pathway that predisposes patients to Alzheimer's disease. Elevated CypA concentrations in pericytes cause nuclear translocation of NF- $\kappa$ B and increase the activation

of matrix metalloproteinase-9 (MMP-9) (30). In this study, the serum CypA levels of patients in the research group were significantly higher than those of the control group, suggesting that traumatic brain injury could cause the brain tissue to release a large amount of CypA, which might participate in the secondary inflammatory response. In the logistic regression model and the Kaplan-Meier survival curves, it was found that the survival time of the group with elevated CypA levels was significantly reduced, and the abnormal increase in levels was an independent risk factor that affected the prognosis of patients with severe head injury and delirium who were transferred out of the ICU. These results indicated that serum CypA had a strong predictive ability for the prognosis of ICU patients with severe head injury and delirium combined with multiple injuries.

In summary, the serum levels of S100B, NSE, and CypA are closely related to the prognosis of patients with delirium transferred out of the ICU with severe craniocerebral injury. They can be used as molecular markers for predicting the prognosis of patients, and may serve as potential targets for treatment.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/apm-21-424>

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-21-424>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Sichuan Provincial People's Hospital, University of Electronic

Science and Technology of China (No. 20171208). All patients agreed to participate in this study and signed an informed consent form.

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