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EXPRESSION AND DIAGNOSTIC VALUE OF GFAP, NSE COMBINED WITH S100β IN PATIENTS WITH SEPSIS-RELATED ENCEPHALOPATHY

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Abstract: To study the expressions of glial fibrillary acidic protein (GFAP), Neuron-specific en ase (NSE) combined with S100β in patients with sepsis-associated encephalopathy (SAE) and their diagnostic value. Methods: A total of 186 sepsis patients admitted to the ICU of our hospital from January 2019 to January 2022 were selected and divided into the SAE group of 86 cases and the non-SAE group of 100 cases according towhether the patients had SAE or not. The clinical data (general data, laboratory indicators) of the two groups were collected, serum GFAP, NSE, And S100β levels were determined, and the degree of brain injury was evaluated according to the Glasgow Coma Scale (GCS), and the 28-day prognosis and survival of the patients were analyzed. The ROC curve was used to analyze the predictive value of GFAP, NSE and S100β on the occurrence of the same. Logistic regression was used to analyze the factors affecting the occurrence of SAE. Results: The levels of GFAP, NSE and S100β were higher than those in the non-SAE group (P<0.05). Logistic regression analysis showed that combined hyperuricemia, high Hcy, high SOFA score, high APACHE II score, high PCT level, high CRP level, high GFAP level, high NSE level, High S100β level was associated with the occurrence of SAE (P <0.05). The 28-day mortality in the SAE group was higher than that in the non-SAE group [31.40% (27/86) vs 10.00% (10/100)] ($\chi 2$=13.282, P < 0.05). With the aggravation of brain injury in SAE patients, the levels of GFAP, NSE, And S100β gradually increased. Pearson correlation analysis showed that the levels of GFAP, NSE and S100β were correlated with the degree of brain injury in SAE patients (P<0.05). The levels of GFAP, levels of GFAP, NSE and S100β in SAE death patients were higher than those in surviving patients (P<0.05) showing that the levels of GFAP, NSE and S100β were associated with the 28-day prognosis of SAE patients (P<0.05). The ROC curve showed that GFAP, NSE combined with S100βhad better diagnostic value for SAE (AUC=0.934, 95%CI=0.796-0.962, P < 0.05) Pearson correlation analysis showed that GFAP was positively correlated with NSE (r=0.453, P<0.05). GFAP was positively correlated with S100β (r=0.443, P < 0.05); NSE was positively correlated with S100β (r=0.620, P < 0.05). The occurrence of SAE is affected by a variety of factors. GFAP, NSE, and S100β are elevated in this disease and are related to the degree of brain injury and prognosis of patients. When the level is ≥0.56 mg/L, it indicates a higher risk of SAE and can be used for early diagnosis of this disease.

Keywords: Glial fibrillary autoprotein; Neuron-specific enolase; According to beta protein; Sepsis-associated encephalopathy

INTRODUCTION

Sepsis-associated encephalopathy (SAE) is a serious complication of sepsis, which is initiated by a systemic inflammatory cascade during the development of sepsis, according to the investigation (Tauber et al. 2021; Molnar et al. 2018). SAE occurs in about 50% of patients with sepsis, and its mortality is increasing year by year, which threatens the life safety of patients to a certain extent. Although most reports have found that the occurrence of SAE is related to the joint action of various factors, the specific mechanism of SAE is still completely clear, as shown by some studies (Guo et al. 2021; Yan et al. 2019). Some studies have shown that the occurrence of SAE is related to the expression changes of various brain injury markers, such as GFAP, NSE, S100β, etc. However, the role of GFAP, NSE, and S100β in the development of SAE and their diagnostic value for the disease are few and still need to be further explored. In this study, SAE patients were selected as subjects to analyze whether GFAP, NSE, S100β and other brain injury markers could be used for the early diagnosis of SAE, to provide a reference for the diagnosis of clinical SAE.

1.2 Methods

1.2.1 Clinical Data

A total of 186 patients with sepsis admitted to the ICU of our hospital from January 2019 to January 2022 were selected. The inclusion criteria were as follows: they met the sepsis 3.0 diagnostic criteria issued by the American Society of Critical Care Medicine (Napolitano, 2018). Patients with primary infection or bacteremia and two of the following conditions can be diagnosed: ① body temperature < 36℃ or 38℃; ② Heart rate 90 beats /min; ③ arterial partial pressure of carbon dioxide < 32mmHg or respiratory rate 20 beats /min; ④ White blood cell count (WBC) 12×109/ L or < 4.0 x 109/ L. According to whether the patient conforms to Robba et al. (2018). According to the proposed SAE diagnostic criteria, the patients were divided into the SAE group (86 cases) and the non-SAE group (100 cases). Exclusion criteria: Brain injury other than sepsis, such as hepatic encephalopathy, central nervous system infection, acute poisoning, etc., were excluded in SAE patients. The hospital stay was less than 24 hours; Patients with mental illness; Persons under 18 years of age; Patients with malignant tumors; Heart failure; Patients with incomplete clinical data.

1.2.2 Clinical data collection

General data and laboratory indicators of all subjects were collected. General information includes gender, age, body mass index (BMI), body temperature, heart rate, breathing rate, long history, long-term smoking, drinking complications (high blood pressure, diabetes, coronary heart disease), the source of infection, the respiratory system, circulatory system, urinary system, digestive system, other), whether high uric acid, whether the combining high Hcy levels, the sequential organ failure assessment (SOFA score, Acute Physiology and Chronic Health Evaluation System ii (APACHE ii) score. Laboratory parameters included procalcitonin (PCT), C-reactive protein (CRP), WBC, platelet count (PLT), calcium (Ca)2+), potassium (K+), aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine (SCr), blood urea nitrogen (BUN), total bilirubin (TBil), total cholesterol (TC), fasting blood glucose (FBG).

1.2.3 Determination of GFAP, NSE and S100β levels

Three ml venous blood samples were collected from all patients within 24 hours after admission to ICU. Serum GFAP, NSE and S100β levels were measured by enzyme-linked immunosorbent assay (ELISA). Absorbance was measured at 450nm wavelength (reference wavelength 570-630nm). The serum levels of GFAP, NSE and S100β were calculated by drawing standard curves. ELISA kits and related reagents were provided by Beckman Coulter Co., LTD.

1.2.4 Evaluation of the degree of brain injury

The Glasgow Coma Scale (GCS) was used to evaluate the degree of brain injury. The total score was speech response, motor response and eye-opening. The GCS score ranged from 3 to 5, including 13-15 as mild brain injury, 9-12 as moderate brain injury, and < 8 as severe brain injury.

1.2.5. Prognosis evaluation at 28d

The 28d prognostic survival was compared between the SAE group and non-SAE group, and the relationship between GFAP, NSE and S100β levels and 28d prognostic survival was analyzed.

1.3 Statistical analysis

SPSS 22.0 was used for data analysis. Measurement data conforming to normal distribution were described by mean ± standard deviation (), and an independent sample t-test was used for comparison between the two groups. $\bar{x} \pm s$ The enumeration data were expressed as a percentage (%)χ2Inspection.ROC curve was used to analyze the predictive value of GFAP, NSE and S100β for SAE. Pearson correlation analysis was used to analyze the correlation between GFAP, NSE and S100β. Logistic regression analysis was used to analyze the factors affecting the occurrence of SAE.Log-rank test was used for survival analysis. $P < 0.05$ was considered statistically significant.

RESULTS

2.1 Comparison of general data between the SAE group and non-SAE group

The gender, age, BMI, body temperature, heart rate, respiratory rate, long-term drinking history, long-term smoking history, hypertension, diabetes, coronary heart

disease, infecti-on source and other data were not significantly compared between SAE group and non-SAE group (P≥0.05). The incidences of hyperuricemia, hyperglycemia, SOFA score and APACHE ii score in the SAE group were higher than those in the non-SAE group (P < 0.05) (table 1).

2.2 WBC, PLT, and Ca in SAE group and non-SAE group2+

The levels of SCr, BUN, TBil, TC and FBG were not significantly compared (P<0.05). The levels of PCT, CRP, AST, and ALT between the SAE group and non-SAE group were higher than those in a non-SAE group (P<0.05) shown in table (2).

2.3 Comparison of GFAP, NSE, and S100β levels

Comparison of GFAP, NSE and S100β between SAE group and non-SAE group (P < 0.05) shown in (Table 3 and Figure 1).

2.4 Logistic Multivariate analysis affecting the occurrence of SAE

The indicators with differences in the above table were included in the Logistic regression equation as independent variables, and SAE was used as the dependent variable (occurrence =1, non-occurrence =0). The results showed that, the results showed that hyperuricemia, hyperhcysemia, SOFA score, APACHE ii score, PCT level, CRP level, GFAP level, NSE level and S100β level were associated with SAE (P < 0.05) table (4).

2.5 Comparison of 28d prognostic survival between SAE group and non-SAE group

The 28d prognostic mortality rate of SAE group was higher than that of non-SAE group [31.40% (27/86) vs 10.00% (10/100)] (χ2=13.282, P < 0.05) shown in figure (2).

2.6 Comparison of the levels of GFAP, NSE, and S100β in SAE patients with different degrees of brain injury

The levels of GFAP, NSE, and S100β gradually increased with the aggravation of brain injury in SAE patients, and the levels of severe brain injury were higher than those of moderate brain injury and mild brain injury (P < 0.05) (Table 5 and Figure 3). Pearson correlation analysis showed that the levels of GFAP, NSE and S100β were correlated with the degree of brain injury in SAE patients (P < 0.05) (figure 4).

2.7 Comparison of levels of GFAP, NSE, and S100β in SAE patients with different prognoses

The levels of GFAP, NSE, and S100β in SAE dead patients were higher than those in survival patients (P < 0.05).See Table 6 and Figure 5.Pearson correlation analysis showed that the levels of GFAP, NSE and S100β were correlated with the 28d prognosis of SAE patients (P < 0.05) figure (6).

2.8 The diagnostic value of GFAP

NSE combined with S100β for SAE showed that GFAP, NSE combined with S100β had better diagnostic value for SAE (AUC=0.934, 95%CI= 0.796-0.962, P < 0.05) (Table 7 and Figure 7).

2.9 Correlation analysis of GFAP, NSE, and S100β

Pearson correlation analysis showed that GFAP was positively correlated with NSE (r=0.453, P < 0.05). GFAP was positively correlated with S100β (r=0.443, P < 0.05). NSE was positively correlated with S100β (r=0.620, P < 0.05) figure (8).

Table 1 Comparison of general data between the SAE group and non-SAE group

		SAE group (n=86)	Non-SAE group (n=100)	χ2/t	P
gender	Male	51 (59.30)	54 (54.00)	0.53	0.47
	Female	35 (40.70)	46 (46.00)		
Age (years)		55.45±6.71	55.48±6.89	0.03	0.98
BMI (kg/m2)		24.53±2.19	24.38±3.32	0.36	0.72
Temperature anomalies		13 (15.12)	20 (20.00)	0.76	0.38
The heart rate abnormal		17 (19.77)	23 (23.00)	0.29	0.59
Abnormal respiratory rate		11 (12.79)	15 (15.00)	0.19	0.66
The long history of alcohol use		6 (6.98)	10 (10.00)	0.54	0.46
Long-term smoking history		5 (5.81)	8 (8.00)	0.34	0.56
Hypertension		8 (9.30)	14 (14.00)	0.98	0.32
Diabetes		10 (11.63)	15 (15.00)	0.45	0.50
Coronary heart disease (CHD)		9 (10.47)	12 (12.00)	0.11	0.74
The source of infection	The respiratory system	16 (18.60)	14 (14.00)	2.09	0.72
	The circulatory system	16 (18.60)	20 (20.00)		
	Urinary system	23 (26.74)	35 (35.00)		
	The Digestive system	20 (23.26)	21 (21.00)		
	other	11 (12.79)	10 (10.00)		
High uric acid syndrome		25 (29.07)	11 (11.00)	9.67	0.002
High Hcy levels,		28 (32.55)	12 (12.00)	11.58	<0.001
SOFA score (points)		10.12±1.04	8.84±0.25	11.92	<0.001
APACHE ii score (points)		22.35±2.19	18.97±1.03	13.77	<0.001

Table 2 Comparison of laboratory indicators between the SAE group and non-SAE group () $\bar{x} \pm s$

	SAE group (n=86)	Non-sae group (n=100)	T	P
PCT (ng/L)	17.98±2.31	10.03±1.00	31.19	<0.001
CRP (mg/L)	135.63±13.72	120.43±13.47	7.61	<0.001
WBC (x 109/ L)	15.53±2.13	15.67±2.24	0.44	0.66
PLT (x 109/ L)	187.93±20.13	188.12±19.07	0.07	0.945
Ca2+(tendency/L)	2.09±0.67	2.10±0.51	0.12	0.91
K+(tendency/L)	4.11±0.56	4.12±0.78	0.10	0.92
AST (U/L)	143.52±14.79	68.93±6.92	45.04	<0.001
ALT (U/L)	92.32±4.32	50.23±2.91	78.84	<0.001
SCr (mu mol/L)	146.63±16.73	145.98±15.82	0.27	0.79
BUN (tendency/L)	14.52±1.08	14.67±1.11	0.93	0.35
TBil (mu mol/L)	38.72±3.41	38.96±3.52	0.47	0.64
TC (tendency/L)	4.10±0.35	4.03±0.37	1.32	0.19
FBG (tendency/L)	10.92±1.03	10.37±1.12	0.32	0.75

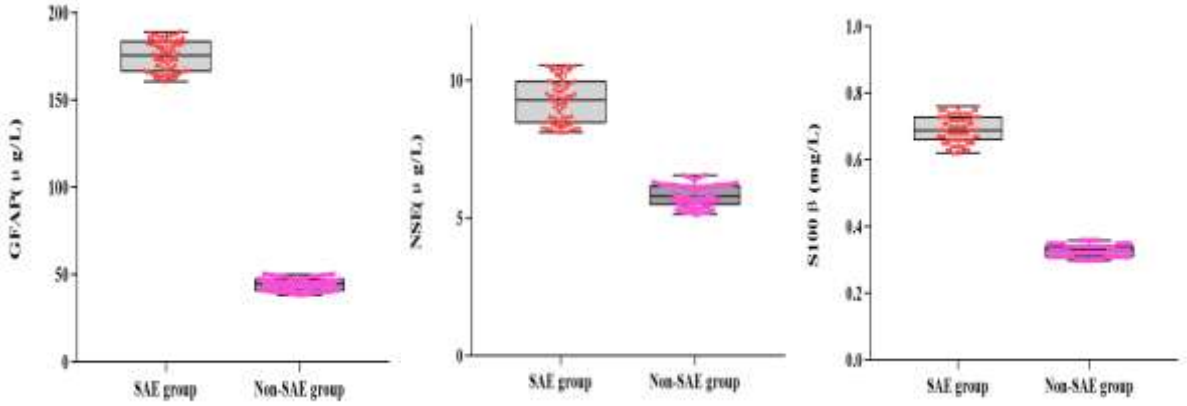

Figure 1 Comparison of the expression of GFAP, NSE and S100β in SAE group and non-SAE group

Table 3 Comparison of GFAP, NSE, and S100β levels between SAE group and non-SAE group () $\bar{x} \pm s$

	SAE group (n=86)	Non-sae group (n=100)	T	P
GFAP (mu g/L)	177.89±14.52	45.61±3.43	88.32	<0.001
NSE (mu g/L)	9.67±1.03	6.05±0.34	33.12	<0.001
According to beta (mg/L)	0.67±0.08	0.33±0.02	41.05	<0.001

Table 4 Logistic multivariate analysis affecting SAE occurrence.

Variable	Beta.	SE	Wald	P	OR (95% CI)
High uric acid syndrome	1.127	0.342	13.452	0.000	3.562 (1.089 to 7.893)
High Hcy levels,	1.225	0.227	12.578	0.000	3.442 (2.003 to 11.371)
SOFA score	1.798	0.242	18.903	0.000	3.706 (2.318 ~ 10.229)
APACHE Ⅱ score	1.667	0.271	20.341	0.000	4.089 (2.001 to 9.085)
PCT	1.352	0.284	4.098	0.025	2.341 (1.089 to 5.893)
CRP	1.224	0.310	5.021	0.014	2.338 (1.002 to 6.332)
AST	1.241	0.893	1.392	0.189	0.897 (0.674-1.438)
ALT	1.363	0.794	1.445	0.113	1.045 (0.896-3.451)
GFAP	1.550	0.325	34.276	0.000	4.589 (2.391 to 10.892)
NSE	1.623	0.332	37.821	0.000	5.004 (1.339 to 11.493)
According to beta.	1.761	0.410	40.932	0.000	5.673 (2.678 to 16.783)

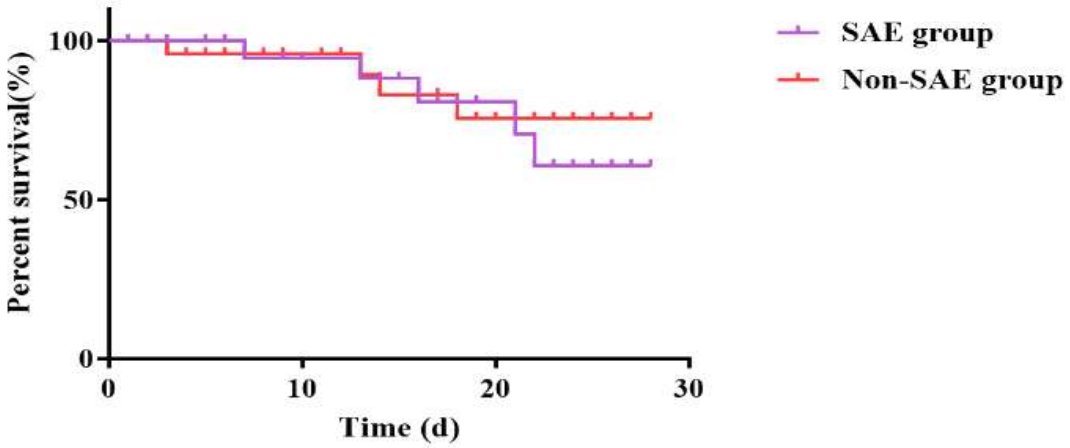

Figure 2 28D survival curves of SAE group and non-SAE group

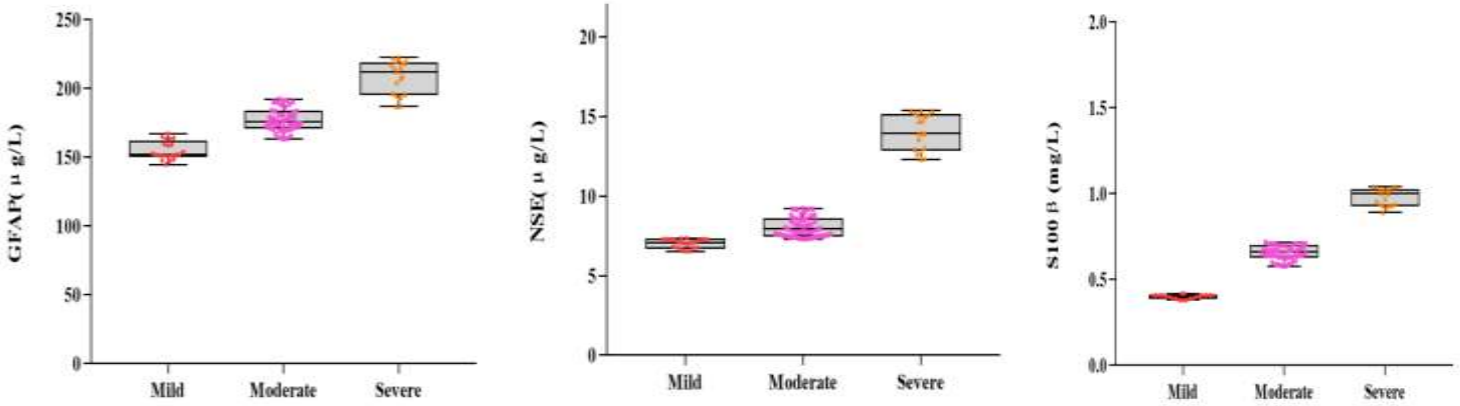

Figure 3 Comparison of expression of GFAP, NSE and S100β in different degrees of brain injury in SAE patients

Table 5 Comparison of GFAP, NSE, and S100β levels in SAE patients with different degrees of brain injury () $\bar{x} \pm s$

	Mild SAE (n=21)	Moderate (n=46)	Severe (n=19)	F	P
GCS score (points)	14.02±0.56	10.23±1.00	5.67±0.78	58.758	< 0.001
GFAP (mu g/L)	152.91±18.92	175.02±18.96	197.07±22.43	10.128	< 0.001
NSE (mu g/L)	6.29±1.00	8.67±1.08	14.14±2.37	20.832	< 0.001
According to beta (mg/L)	0.41±0.04	0.62±0.05	0.95±0.10	34.250	< 0.001

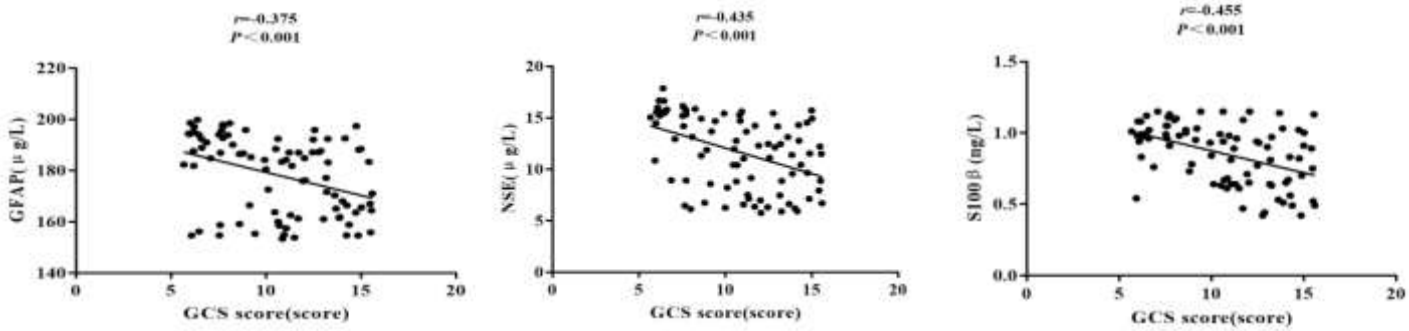

Figure 4 Correlation graph of GFAP, NSE, S100β and brain injury degree in SAE patients

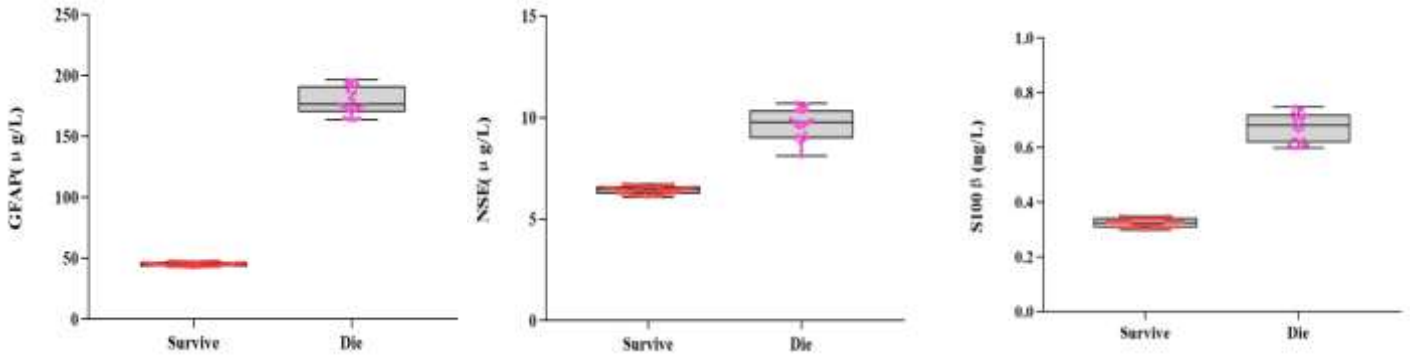

Figure 5 Comparison of the expression of GFAP, NSE and S100β in different prognoses of SAE patients

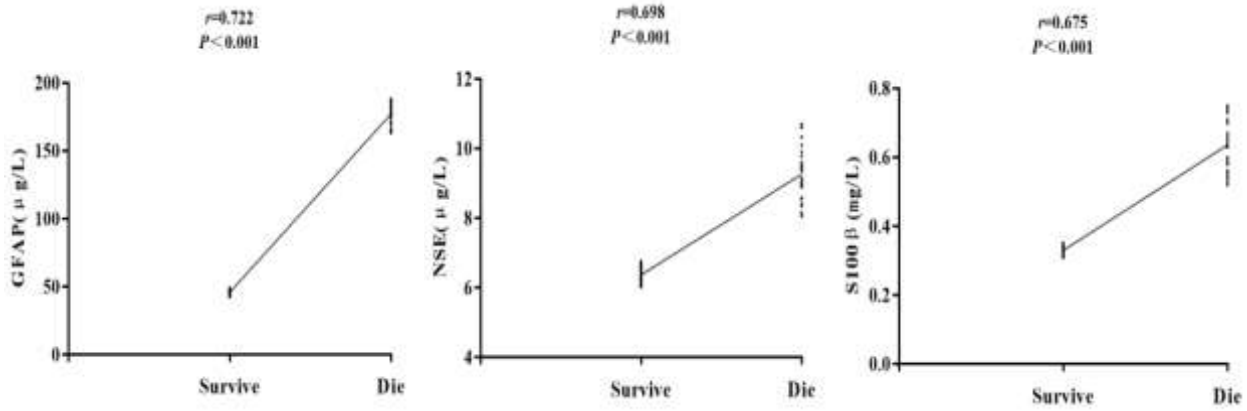

Figure 6 Correlation between GFAP, NSE, S100β and the prognosis of SAE patient

Table 6 Comparison of GFAP, NSE, and S100β levels in SAE patients with different prognoses () $\bar{x} \pm s$

	Survival (n=59)	Death (n=27)	t	P
GFAP (mu g/L)	45.61±3.43	177.89±14.52	66.460	< 0.001
NSE (mu g/L)	6.05±0.34	9.67±1.03	24.390	< 0.001
According to beta (mg/L)	0.33±0.02	0.67±0.08	30.800	< 0.001

Table 7 Diagnostic efficiency analysis of GFAP and NSE combined with S100β for SAE

	The critical value	Sensitivity (%)	Specificity (%)	AUC	95%CI	P
GFAP	123.31 mu g/L	86.75	72.41	0.865	0.624 ~ 0.945	0.001
NSE	7.89 mu g/L	85.50	74.54	0.831	0.613 ~ 0.984	0.001
According to beta.	0.56 mg/L	83.42	77.68	0.827	0.656 ~ 0.945	0.002
GFAP+NSE+according to beta	-	90.89	70.32	0.934	0.796 ~ 0.962	0.000

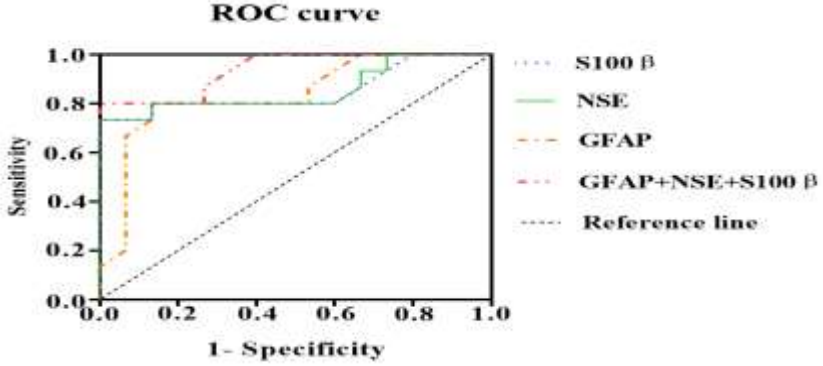

Figure 7 ROC curve of GFAP, NSE combined with S100β in the diagnosis of SAE

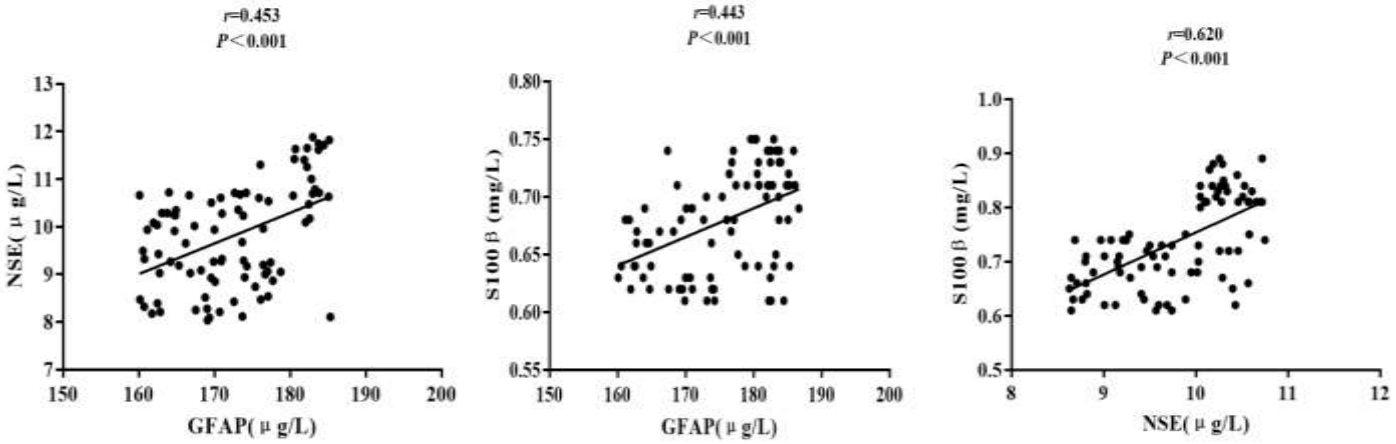

Figure 8 Correlation diagram between GFAP, NSE, and S100β

DISCUSSION

SAE is a common metabolic encephalopathy, which is mainly diagnosed by excluding other causes. At present, the diagnosis of SAE in clinical practice mostly relies on MRI, CCT, GCS score or electroencephalogram functional examination. Although there is a certain detection rate, there is still a phenomenon of missed diagnosis, and lack of sensitivity serum indicators measurement. The results of this study showed that: In addition to hyperuricemia, hyperglycemia, high SOFA score, high APACHE ii score, high PCT level, and high CRP level, high GFAP level, high NSE level, and high S100β level were associated with the occurrence of SAE. The results suggested that GFAP, NSE, and S100β may be involved in the occurrence and progression of SAE.

Reports suggest (Anderson et al. 2020; Seidenfaden et al. 2021), astrocytes about 20 ~ 40% of the human brain, it is a basic frame of the central nervous system, involved in signal transduction and deal with the central nervous system, and GFAP as the central nervous system related proteins, the brain is unique, in astrocyte injury or death after a large number of releases, its content increased often marks the brain damage (Wu et al. 2019). A study showed that serum levels of GFAP were increased in patients with SAE, and early elevation of serum GFAP was associated with poor prognosis and quality of life. Other study (Hua et al. 2019) have shown that, astrocytes as one of the most abundant brain glial cells, reactive astrocyte proliferation on the central nervous system disease pathological reaction specificity with specific diseases and disease stage, and the changing functions of the astrocytes is of great significance for the detection and prognosis of SAE, the study found that the main composition of GFAP astrocytes as a skeleton, Gfap is a major component of astrocytoskeleton, and its content is increased in this disease. The results of this study showed that the expression of GFAP was increased in SAE, and the increase was aggravated with the progression of the disease, which was consistent with the above reports. The reason may be related to the functional damage of astrocytes during the occurrence of SAE, and the massive synthesis and secretion of GFAP as a component of astrocyte skeleton in order to repair the damage. Finally, high expression of GFAP in SAE was observed.

NSE is an intracytoplasmic glycosylase, which is mainly distributed in neuroendocrine tissues and neurons. If the content of NSE increases after nerve tissue injury and neuronal apoptosis, the content of NSE in peripheral blood will increase accordingly (Li et al. 2021; Czupryna et al. 2018; Yuan et al. 2019). The study of Park et al. (2019) found that in the process of sepsis, many inflammatory mediators in the body stimulate the brain, and brain cells react to inflammatory mediators, leading to tissue damage. Currently, NSE is oversecreted to resist inflammatory invasion and repair brain damage. A study (Ehler et al. 2019) showed that NSE was oversecreted in SAE, there was no difference in NSE content between SAE patients and non-SAE patients. However, in this study, it was found that the content of NSE in serum of SAE patients was significantly higher than that of non-SAE patients, which was contrary to the above reports. The reasons may be related to the differences in sample size and population. While Yao et a. (2014) found that serum NSE content was increased in SAE patients, which was consistent with the results of this study.

S100 protein is a small molecule protein, and S100β is an important monomer of S100 protein. As a family of intracellular calcium-binding proteins, S100β is mainly distributed in astrocytes around mature blood vessels in the central nervous system (Wang et al. 2019; Duan et al. 2021; Hanin et al. 2022). In response to neuronal injury or pathological changes in brain tissue, astrocytes release a large amount of S100β protein stored in astrocytes, and the amount of S100β protein released gradually increases with the aggravation of brain injury. Zhang et al. (2022) reports that in brain injury caused by inflammatory cascade, a large amount of S100β protein is synthesized in the body, which is released into the blood during the

progression of the disease, leading to the increase of S100β protein content in peripheral blood. At present, with the gradual in-depth clinical research on the S100β protein, it has been found that it can regulate brain cell energy metabolism, glial cell differentiation, neuronal differentiation and so on. Deng et al. (2021) experiments showed that the expression of S100β protein was abnormally high in the process of brain dysfunction in sepsis, and the level of S100β protein was significantly decreased after drug intervention, suggesting that the drug intervention inhibited the synthesis and secretion of S100β protein by alleviating the local inflammatory cascade, and finally repaired the brain injury. The results of this study showed that compared with patients without SAE, the expression of S100β protein in the peripheral blood of SAE patients was significantly increased, and the expression of S100β protein was more aggravated with the aggravation of brain injury. The results suggested that S100β protein may be involved in the progression of SAE, and the reason may be related to the excessive secretion of S100β protein induced by inflammatory injury.

In this study, the expression of GFAP, NSE and S100β in patients with different prognosis was further analyzed. The results showed that the expressions of GFAP, NSE and S100β were significantly higher in the dead patients than in the surviving patients, and the correlation analysis showed that the three proteins were clearly correlated with the prognosis of the patients. These results suggest that GFAP, NSE, and S100β can not only be used as diagnostic indicators for SAE, but also be used to evaluate the prognosis of SAE patients. In addition, the correlation between GFAP, NSE and S100β was found to be positively correlated, suggesting that the three have a certain relationship in the process of SAE, which is related to the injury of brain tissue after the occurrence of SAE, and then affect the mutual expression of indicators.

CONCLUSION

It is concluded that the occurrence of SAE is affected by many factors. GFAP, NSE, and S100β are increased in this disease and are related to the degree of brain injury and prognosis of patients. GFAP level ≥123.31 μg/L, NSE level ≥7.89 μg/L, and S100β level ≥0.56 mg/L indicate a high risk of SAE, which can be used for early diagnosis of SAE. However, there are still some shortcomings in this study. For example, the specific mechanism of the influence of GFAP, NSE and S100β on the occurrence of SAE was not systematically analyzed, and the expression of GFAP, NSE and S100β in serum was only analyzed, and the expression of the three in cerebrospinal fluid was not further analyzed.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

All the authors contributed equally in conducting research, writing the article and analyzing data.

REFERENCES

Anderson TN, Hinson HE, 2020. Damaged: Elevated GFAP and UCH-L1 as the Black Flag of Brain Injury. Resuscitation 154:110-1.

Czupryna P, Grygorczuk S, Pancewicz S, Świerzbińska R, Zajkowska J, Krawczuk K, Dunaj J, Filipiuk J, Kruszewska E, Borawski K, Moniuszko-Malinowska A, 2018. Evaluation of NSE and S100B in patients with tick-borne encephalitis. Brain Behav 8(12):e01160.

Deng X, Zou Q, Zheng S, Wang H, 2021. Protective effect and mechanism of Angong Niuhuang pill in sepsis-associated brain dysfunction of rats. Zhonghua wei Zhong Bing ji jiu yi xue 33(8):979-84.

Duan K, Liu S, Yi Z, Liu H, Li J, Shi J, Ji L, Xu B, Zhang X, Zhang W, 2021. S100-β aggravates spinal cord injury via activation of M1 macrophage phenotype. J Musculoskelet Neuronal Interact 21(3):401.

Ehler J, Saller T, Wittstock M, Rommer PS, Chappell D, Zwissler B, Grossmann A, Richter G, Reuter DA, Noeldge-Schomburg G, Sauer M, 2019. Diagnostic value of NT-proCNP compared to NSE and S100B in cerebrospinal fluid and plasma of patients with sepsis-associated encephalopathy. Neurosci Let 692:167-73.

Guo W, Li Y, Li Q, 2021. Relationship between miR-29a levels in the peripheral blood and sepsis-related encephalopathy. Am J Transl Res 13(7):7715.

Hanin A, Denis JA, Frazzini V, Cousyn L, Imbert-Bismut F, Rucheton B, Bonnefont-Rousselot D, Marois C, Lambrecq V, Demeret S, Navarro V, 2022. Neuron Specific Enolase, S100-beta protein and progranulin as diagnostic biomarkers of status epilepticus. J Neurol 21:1-9.

Hua X, Wang Y, Yang C, Chai R, Li X, Tayier G, Pan P, Yu X, 2019. Effect of incubation with lipopolysaccharide and interferon-γ on reactive astrogliosis. J Integ Neurosci 18(4):415-21.

Li M, Ye M, Zhang G, 2021. Aberrant expression of miR-199a in newborns with hypoxic-ischemic encephalopathy and its diagnostic and prognostic significance when combined with S100B and NSE. Acta Neurologica Belgica 121(3):707-14.

Molnar L, Fülesdi B, Németh N, Molnár C, 2018. Sepsis-

associated encephalopathy: A review of literature. Neurol India 66(2):352.

Napolitano LM, 2018. Sepsis 2018: definitions and guideline changes. Surg infect 19(2):117-25.

Park DW, Park SH, Hwang SK,2019. Serial measurement of S100B and NSE in pediatric traumatic brain injury. Child's Nerv Sys 35(2):343-8.

Robba C, Crippa IA, Taccone FS, 2018. Septic encephalopathy. Cur neurol neurosci rep 18(12):1-9.

Seidenfaden SC, Kjerulff JL, Juul N, Kirkegaard H, Møller MF, Münster AM, Bøtker MT, 2021. Diagnostic accuracy of prehospital serum S100B and GFAP in patients with mild traumatic brain injury: a prospective observational multicenter cohort study–"the PreTBI I study". Scand J Trauma Resusc Emerg Med 29(1):1-0.

Tauber SC, Djukic M, Gossner J, Eiffert H, Brück W, Nau R, 2021. Sepsis-associated encephalopathy and septic encephalitis: an update. Expert Rev Anti Infect Ther 19(2):215-31.

Wang Y, Hou Y, Li H, Yang M, Zhao P, Sun B, 2019. A SERS-based lateral flow assay for the stroke biomarker S100-beta (Retraction of Vol 186, art no 548, 2019).

Wu L, Ai ML, Feng Q, Deng S, Liu ZY, Zhang LN, Ai YH, 2019. Serum glial fibrillary acidic protein and ubiquitin C-terminal hydrolase-L1 for diagnosis of sepsis-associated encephalopathy and outcome prognostication. J Crit Care 52:172-9.

Yan S, Gao M, Chen H, Jin X, Yang M, 2019. Expression level of glial fibrillary acidic protein and its clinical significance in patients with sepsis-associated encephalopathy. Zhong nan da xue xue bao. Yi xue ban= J Cent South Univ Med Sci 44(10):1137-42.

Yao B, Zhang LN, Ai YH, 2014. Serum S100β is a better biomarker than neuron-specific enolase for sepsis-associated encephalopathy and determining its prognosis: a prospective and observational study. Neurochem res 39(7):1263-9.

Yuan X, Wang J, Wang D, Yang S, Yu N, Guo F, 2019. NSE, S100B and MMP9 expression following reperfusion after carotid artery stenting. Cur Neurovas Res 16(2):129-34.

Zhang Y, Jiang L, Han Y, 2022. Reduced Concentrations of NSE, S100β, Aβ, and Proinflammatory Cytokines in Elderly Patients Receiving Ultrasound-Guided Combined Lumbar Plexus-Sciatic Nerve Block during Hip Replacement. Genet Res 11.