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Prognostic values of tumor necrosis factor-alpha, monocyte chemoattractant protein-1, and neuron-specific enolase in patients with sepsis-associated encephalopathy

Prognostička vrednost faktora nekroze tumora alfa, monocitnog hemoatraktantnog proteina-1 i neuron-specifične enolaze kod bolesnika sa encefalopatijom izazvanom sepsom

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Abstract

Background/Aim. Sepsis-associated encephalopathy (SAE) is a severe complication of sepsis, characterized by brain dysfunction and associated with a poor prognosis. SAE has a complex pathogenesis, and its severity is in close association with the levels of various serum factors. The aim of the study was to investigate the correlation of tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1, and neuron-specific enolase (NSE) levels with the severity of SAE and to analyze the prognostic values of the three parameters. **Methods**. This prospective study enrolled 126 patients treated for SAE from June 2020 to June 2022. The levels of TNF-α, MCP-1, and NSE were measured, and the severity of SAE was evaluated using the Sequential Organ Failure Assessment (SOFA) score. Based on the SOFA score, the patients were assigned to two groups: a group with a bad prognosis and a group with a good prognosis. The correlations of TNF-α, MCP-1, and NSE levels with the severity of SAE were analyzed, and their prognostic values were evaluated during a 28-day follow-up. **Results**. The mean levels of TNF-α, MCP-1, and NSE and the SOFA score of the 126 patients with SAE were 6.52 ± 1.48 pg/mL, 62.53 ± 18.49 pg/mL, 8.61 ± 2.17 ng/mL, and 10.24 ± 2.86 points, respectively. Pearson's analysis demonstrated significant correlations between TNF-α, MCP-1, and NSE levels and the SOFA score of patients with SAE ($r > 0$, $p < 0.05$). Of the 126 patients, 61 (48.4%) had a poor prognosis, while 65 (51.6%) had a good prognosis. Increased serum TNF-α, MCP-1, and NSE levels were risk factors for the poor prognosis of patients with SAE [odds ratio (OR) > 1, $p < 0.05$]. The areas under the receiver operating characteristic (ROC) curves of serum TNF-α, MCP-1, and NSE levels were all > 0.7, suggesting high predictive values of these parameters. **Conclusion**. Serum TNF-α, MCP-1, and NSE levels are closely correlated with the severity of SAE and may work as valuable predictors of treatment outcome.

Key words:
correlation of data; monocyte chemoattractant protein-1; prognosis; risk factors; sepsis associated encephalopathy; tumor necrosis factor-alpha; neuron-specific enolase.

Apstrakt

Uvod/Cilj. Encefalopatija izazvana sepsom (EIS) je teška komplikacija sepse, koju karakteriše disfunkcija mozga, a povezana je sa lošom prognozom. Patogeneza EIS je složena, a težina njene manifestacijhe je u bliskoj korelaciji sa nivoima različitih faktora u serumu. Cilj rada bio je da se ispita korelacija nivoa faktora nekroze tumora (*tumor necrosis factor*-TNF)-α, monocitnog hemoatraktantnog proteina (*monocyte chemoattractant protein*-MCP)-1 i neuron-specifične enolaze (NSE) sa težinom EIS i analizira prognostička vrednost ova tri parametra. **Metode.** Ovom prospektivnom studijom obuhvaćena su 126 bolesnika sa EIS, lečena u periodu od juna 2020. do juna 2022. godine. Određivani su nivoi TNF-α, MCP-1 i NSE, a težina EIS procenjena je korišćenjem skora procene sekvencijalnog popuštanja organa (*Sequential Organ Failure Assessment* – SOFA). Na osnovu SOFA skora, bolesnici su podeljeni u dve grupe – grupu sa lošom prognozom i grupu sa dobrom prognozom. Analizirane su korelacije nivoa TNF-α, MCP-1 i NSE sa težinom EIS, a njihove prognostičke vrednosti procenjivane su tokom 28-dnevnog praćenja. **Rezultati.** Prosečni nivoi TNF-α, MCP-1, NSE i SOFA skora kod 126 bolesnika sa EIS bili su 6,52 ± 1,48 pg/mL, 62,53 ± 18,49 pg/mL, 8,61 ± 2,17 ng/mL i 10,24 ± 2,86 poena, redom. Pirsonova analiza pokazala je značajne korelacije između nivoa TNF-α, MCP-1 i

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NSE i SOFA skora bolesnika sa EIS ($r > 0$, $p < 0,05$). Od 126 bolesnika, njih 61 (48,4%) imalo je lošu prognozu, dok je njih 65 (51,6%) imalo dobru prognozu. Faktori rizika za lošu prognozu kod bolesnika sa EIS bili su povišeni nivoi TNF-α, MCP-1 i NSE u serumu [*odds ratio* (OR) > 1, $p < 0,05$]. Površine ispod *receiver operating characteristic* (ROC) krive za TNF-α, MCP-1 i NSE u serumu bile su > 0,7, što ukazuje na visoke prognostičke vrednosti tih parametara. **Zaključak.** Nivoi TNF-α, MCP-1 i NSE usko su povezani sa težinom EIS i mogu biti vredni prediktori ishoda lečenja.

Ključne reči:
podaci, korelacija; monocitni hemoatraktantni protein-1; prognoza; faktori rizika; encefalopatija izazvana sepsom; faktor nekroze tumora – alfa; neuron-specifična enolaza.

Introduction

Sepsis-associated encephalopathy (SAE) is a severe complication of sepsis, characterized by brain dysfunction and associated with a poor prognosis [1]. As a critical disease, SAE can cause sudden and severe chills, high fever, a series of uncomfortable symptoms in the central nervous system, secondary epilepsy, as well as respiratory, circulatory, and renal failure [2, 3]. The treatment of SAE is difficult, so the hospitalization stay is prolonged, and the mortality rate of septic patients is elevated [4]. Moreover, SAE has a complex pathogenesis, and its severity is closely related to the levels of various serum factors [5]. Therefore, it is of guiding significance to identify relevant serum markers for early evaluation of the severity and prognosis of SAE for clinical treatment.

Tumor necrosis factor (TNF)-α is a well-established pro-inflammatory cytokine with a pivotal role in the pathogenesis of sepsis and the inflammatory response of SAE. TNF-α can stimulate the generation of inflammatory transmitters and affect the release of inflammatory cells, making it a useful indicator for evaluating the severity of SAE [6]. Georgescu et al. [7] reported that TNF-α can be used as a predictor of sepsis susceptibility and progression. Monocyte chemoattractant protein (MCP)-1 is a chemotactic cytokine closely related to brain tissue injury, which can exert a chemotactic effect on T lymphocytes, cause neutrophil aggregation, and increase inflammatory mediators, thus worsening brain tissue injury [8]. Chen et al. [9] reported that MCP-1 was a potential marker for patients with sepsis. Neuron-specific enolase (NSE), a biomarker of brain injury, is frequently used in the clinical diagnosis of hypoxic-ischemic encephalopathy and brain injury. Shaik et al. [10] found that NSE was a marker of neuronal damage in patients with epileptic seizures. Thus, NSE may also be associated with SAE [11].

Having all this in perspective, the aim of this study was to investigate the association between TNF-α, MCP-1, and NSE levels and the severity of SAE. Additionally, the predictive value of the three indicators was analyzed in order to provide references for the evaluation of SAE severity and prognosis of disease outcomes.

Methods

A prospective study was conducted on 126 patients with SAE from June 2020 to June 2022, including 69 males and 57 females aged 56–73 years, with an average ± standard deviation (SD) age of 65.3 ± 4.6 years. The body mass index (BMI) was 19–30 kg/m^2, and the average ± SD value was 25.9 ± 2.4 kg/m^2.

The inclusion criteria were as follows: (1) patients who met the relevant diagnostic criteria for SAE (serious infections, such as abdominal infection and sepsis, as well as abnormal symptoms of the central nervous system, such as disturbance of consciousness and decreased orientation) [12], (2) duration of symptoms from onset to admission ≤ 48 hrs, and (3) patients with signed informed consent form. The exclusion criteria involved: (1) cerebrovascular accidents, (2) metabolic encephalopathy, (3) intracranial organic lesions, (4) central nervous system infection, (5) patients who died within 24 hrs after admission, (6) patients who used high-dose hormone drugs in the past one month, (7) acquired immunodeficiency syndrome-AIDS, viral hepatitis, or other severe infectious diseases, (8) hematological diseases or malignancies, and (9) those who gave up treatment halfway and discharged themselves from the hospital.

On admission, 4 mL of venous blood was drawn from each patient and centrifuged at 3,500 rpm for 10 min to separate serum. Then, the levels of serum TNF-α and MCP-1 were measured by enzyme-linked immunosorbent assay, and the NSE level was measured using an automated chemiluminescence immunoassay analyzer (Beckman Coulter, UniCel DxI 800 Access). The severity of the disease was assessed using the Sequential Organ Failure Assessment (SOFA) [13] scoring system for six organ systems/functions (coagulation, respiratory system, cardiovascular system, liver function, renal function, and central nervous system). With 0–4 points for each of the six functions, the total score range was 0–24 points, and a higher score indicated a more severe organ failure and higher severity of disease.

The prognosis for all patients was observed during a 28-day follow-up period. The patients who survived after 28 days were enrolled in the good prognosis group, while those who died within 28 days were classified in the poor prognosis group. The prognosis was poor in 61 (48.4%) patients and good in 65 (51.6%) patients.

The following indicators were compared between the good prognosis group and the poor prognosis group: gender (male, female), age, BMI, diabetes mellitus (DM) (Yes or No; fasting blood glucose ≥ 7.0 mmol/L or 2 hrs postprandial blood glucose ≥ 11.1 mmol/L was considered DM), hypertension (Yes or No; defined as diastolic blood pressure ≥ 90 mmHg or systolic blood pressure ≥ 140 mmHg measured for three consecutive times on different days), hyperuricemia (Yes or No; defined as blood uric acid > 480 μmol/L in males or > 380 μmol/L in females), coagulation disorders [Yes or No; defined as prolonged thrombin time (reference range – RR: 9.2–11.9 s), activated partial thromboplastin time (RR: 24.1–32.3 s), coagulation time (bleeding time RR: 1–4 min, clotting time

RR: 3–5 min); decreased fibrinogen (RR: 2.2–5.2 g/L), platelets (RR: 130–400 × 10^9/L)], malnutrition (Yes or No; defined as albumin level < 35 g/L), drinking history (Yes or No; defined as average daily alcohol consumption > 20 g in females or > 40 g in males for more than one month, or drinking more than once a month for more than six months), smoking history [Yes or No; defined as a smoking index (number of cigarettes per day × years of smoking) ≥ 200], blood analysis [white blood cell (WBC) count RR: 4.5–11.0 × 10^9/L, hemoglobin RR: 12–18 g/dL, and platelet count], procalcitonin (normal value < 0.1 μg/L), C-reactive protein-CRP (normal value < 1 mg/dL), and serum TNF-α (RR: 0–8.1 pg/mL), MCP-1 (RR: 11–88 pg/mL), and NSE (RR: 0–12.5 ng/mL) levels.

Statistical analysis

Statistical analysis was conducted using SPSS 23.0 software. The continuous data were presented as mean ± SD and analyzed by the *t*-test. The discrete data were shown as numbers (percentages) and compared by the χ^2 test. Pearson's correlation analysis was performed between the levels of TNF-α, MCP-1, and NSE and the SOFA score. Logistic regression analysis was employed to determine the effects of serum TNF-α, MCP-1, and NSE levels on the prognosis of patients with SAE. The predictive values of serum TNF-α, MCP-1, and NSE levels for prognosis were analyzed using receiver operating characteristic (ROC) curves, and the $p < 0.05$ was considered statistically significant.

Results

The mean ± SD SOFA score for all 126 patients with SAE was 10.24 ± 2.86 points. The results of Pearson's correlation analysis showed that the serum levels of TNF-α, MCP-1, and NSE were positively correlated with the SOFA score of patients with SAE ($r = 0.453$, 0.446, and 0.559, respectively; $p < 0.001$).

The levels of WBC count, procalcitonin, CRP, TNF-α, MCP-1, and NSE were higher in the poor prognosis group than those in the good prognosis group ($p < 0.05$). There were no significant differences in gender, age, BMI, DM, hypertension, hyperuricemia, coagulation disorders, malnutrition, drinking history, smoking history, hemoglobin level, and platelet count between the two groups ($p > 0.05$) (Table 1).

Table 1

Clinical data of sepsis-associated encephalopathy patients in good and poor prognosis group

Parameter	Poor prognosis group (n = 61)	Good prognosis group (n = 65)	Statistical value	*p*-value
Gender				
male (n = 69)	35 (57.38)	34 (52.31)	$\chi^2 = 0.326$	0.568
female (n = 57)	26 (42.62)	31 (47.69)		
Age (years)	65.47 ± 4.36	65.18 ± 4.21	$t = 0.432$	0.666
Body mass index (kg/m^2)	26.02 ± 2.28	25.77 ± 2.39	$t = 0.600$	0.550
Diabetes mellitus				
yes (n = 15)	8 (13.11)	7 (10.77)	$\chi^2 = 0.165$	0.685
no (n = 111)	53 (86.89)	58 (89.23)		
Hypertension				
yes (n = 46)	24 (39.34)	22 (33.85)	$\chi^2 = 0.410$	0.522
no (n = 80)	37 (60.66)	43 (66.15)		
Hyperuricemia				
yes (n = 56)	29 (47.54)	27 (41.54)	$\chi^2 = 0.459$	0.498
no (n = 70)	32 (52.46)	38 (58.46)		
Coagulation disorders				
yes (n = 35)	18 (29.51)	17 (26.15)	$\chi^2 = 0.177$	0.674
no (n = 91)	43 (70.49)	48 (73.85)		
Malnutrition				
yes (n = 52)	28 (45.90)	24 (36.92)	$\chi^2 = 1.047$	0.306
no (n = 74)	33 (54.10)	41 (63.08)		
Drinking history				
yes (n = 38)	18 (29.51)	20 (30.77)	$\chi^2 = 0.024$	0.877
no (n = 88)	43 (70.49)	45 (69.23)		
Smoking history				
yes (n=39)	17 (27.87)	22 (33.85)	$\chi^2 = 0.526$	0.468
no (n=87)	44 (72.13)	43 (66.15)		
White blood cells count (×10^9/L)	15.36 ± 3.64	14.12 ± 3.58	$t = 2.083$	0.039
Hemoglobin (g/L)	116.53 ± 12.95	115.84 ± 11.36	$t = 0.318$	0.751
Platelet count (×10^9/L)	208.62 ± 43.25	211.76 ± 42.57	$t = 0.411$	0.682
Procalcitonin (pg/mL)	32.58 ± 6.54	29.75 ± 6.18	$t = 2.497$	0.014
C-reactive protein (mg/dL)	22.18 ± 4.36	20.09 ± 4.52	$t = 2.639$	0.009
TNF-α (pg/mL)	7.22 ± 1.26	5.86 ± 1.32	$t = 5.908$	< 0.001
MCP-1(pg/mL)	71.04 ± 16.37	54.54 ± 15.96	$t = 5.728$	< 0.001
NSE(ng/mL)	9.35 ± 1.96	7.92 ± 1.82	$t = 4.247$	< 0.001

TNF– tumor necrosis factor; MCP – monocyte chemoattractant protein; NSE – neuron-specific enolase.
All values are expressed as numbers (percentages) or mean ± standard deviation.

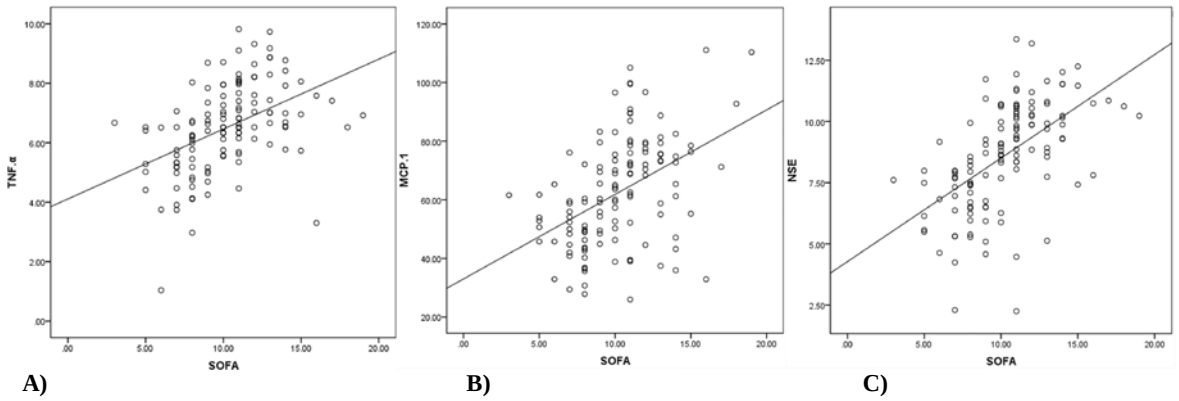
In the 126 patients with SAE, the range of levels of TNF-α was 3.32–10.45 pg/mL, with a mean of 6.52 ± 1.48 pg/mL. The range of MCP-1 levels was 16.42–102.26 pg/mL, with a mean of 62.53 ± 18.49 pg/mL. The range of NSE levels was 4.71–14.30 ng/mL, with a mean of 8.61 ± 2.17 ng/mL. The distribution of the levels according to the severity of SAE is shown in Figure 1.

Effects of serum TNF-α, MCP-1, and NSE levels on the prognosis of patients with SAE

Logistic regression analysis was performed with the levels of TNF-α, MCP-1, and NSE as independent variables (all continuous variables) and the prognosis for patients with SAE as a dependent variable (1 = poor prognosis, 0 = good prognosis). The results showed that the levels of serum TNF-α, MCP-1, and NSE could be considered risk factors for the poor prognosis of patients with SAE (OR > 1, $p < 0.05$) (Table 2 and Figure 2).

Predictive values of serum TNF-α, MCP-1, and NSE levels for the prognosis of patients with SAE

ROC curves were plotted with the levels of TNF-α, MCP-1, and NSE as test variables and the prognosis of patients with SAE as a state variable (1 = poor prognosis, 0 = good prognosis). It was found that the areas under the curves of serum TNF-α, MCP-1, and NSE levels for pre-



A) **B)** **C)**

Fig. 1 – Distribution of TNF-α (A), MCP-1 (B), and NSE (C) levels according to the severity of sepsis-associated encephalopathy (SOFA score).
SOFA – Sequential Organ Failure Assessment. For other abbreviations, see Table 1.

Table 2

TNF-α, MCP-1, and NSE serum levels as risk factors in disease outcome prognosis

Parameter	β	SE	χ^2*	*p*-value	OR	95% CI
TNF-α	0.698	0.198	12.387	< 0.001	2.010	1.363–2.966
MCP-1	0.064	0.016	16.004	< 0.001	1.066	1.033–1.101
NSE	0.442	0.135	10.737	0.001	1.556	1.195–2.028

β – maximum likelihood of estimation coefficient; SE – standard error; OR – odds ratio; CI – confidence interval. For other abbreviations, see Table 1.
***Wald Chi-square distribution.**

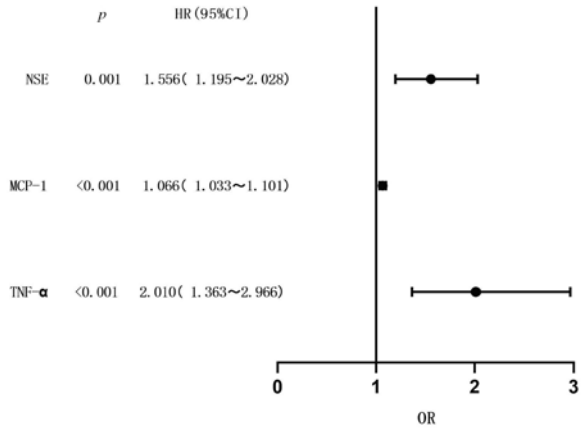


Fig. 2 – A forest plot of multivariate logistic regression analysis for TNF-α, MCP-1, and NSE levels.
HR – hazard ratio. For other abbreviations, see Tables 1 and 2.

Table 3

TNF-α, MCP-1, and NSE serum levels as predictive factors for disease outcome prognosis

Parameter	AUC	SE	*p*-value	95% CI	Cut-off value	Sensitivity	Specificity	Youden index
TNF-α (pg/mL)	0.770	0.042	< 0.001	0.688–0.852	6.48	0.787	0.677	0.464
MCP-1 (pg/mL)	0.761	0.043	< 0.001	0.676–0.845	66.81	0.754	0.754	0.508
NSE (ng/mL)	0.704	0.046	< 0.001	0.614–0.795	8.38	0.705	0.615	0.320
Combined detection	0.809	0.039	< 0.001	0.732–0.886	-	0.836	0.631	0.467

AUC – Area Under the Receiver Operating Characteristic Curve. For other abbreviations, see Tables 1 and 2.

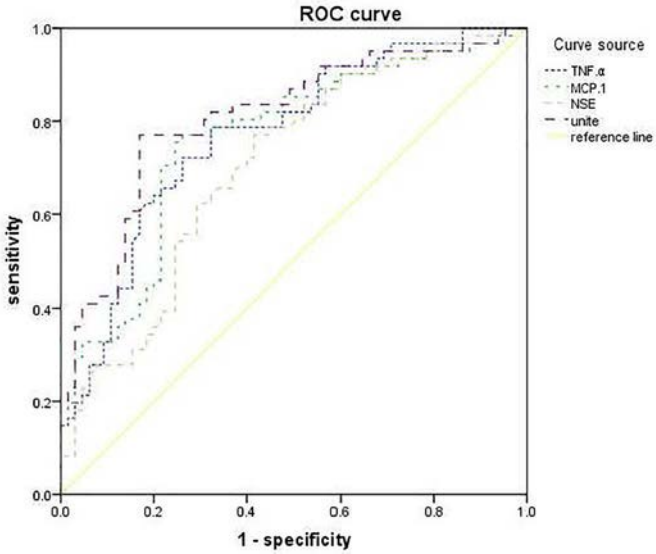


Fig. 3 – Receiver Operating Characteristic (ROC) curves of serum TNF-α, MCP-1, and NSE levels as predictive factors of outcome for patients with SAE. For abbreviations, see Table 1.

dicting the poor prognosis of patients with SAE were all > 0.7, suggesting certain predictive value and the predictive value of combined detection of these three indicators was higher (Table 3 and Figure 3).

Discussion

The underlying pathological mechanism of SAE remains elusive, which may be related to direct nerve injury, oxidative stress injury, inflammatory reaction, etc. [14]. At any stage of sepsis, SAE can occur, and patients mainly present with changes in consciousness, arousal, behavior, and cognition, and deep coma in severe cases [15]. Despite advances in clinical awareness of SAE and treatment methods, the mortality rate of SAE remains high [16]. In this study, 61 out of 126 patients with SAE had a poor prognosis, accounting for 48.4% of the total number of patients, suggesting a high rate of poor prognosis. Therefore, it is of great significance to explore the related indicators of the severity and prognosis of SAE for early evaluation of disease severity and prognostic prediction [17].

At present, many routine detection indicators are available for SAE, including WBC count, procalcitonin, and CRP, which can reflect the inflammatory status of patients to a certain extent [18]. However, the levels of these indicators can also increase to varying degrees in patients with simple sepsis, resulting in low specificity in evaluating SAE. Therefore, there is still a need to explore other detection indicators. Patients with SAE are in a severe stress state that can stimulate the activation of a large number of monocytes, macrophages, neutrophils, etc., and the release of a variety of inflammatory cytokines, including TNF-α [19]. TNF-α is a polypeptide cytokine with various biological activities, including involvement in many pathological and physiological processes, such as inflammatory response and immune defense [20]. In this study, the results of Pearson's correlation analysis showed a positive correlation between the serum TNF-α level and the SOFA score of patients with SAE, indicating that the higher the serum TNF-α level, the more severe the disease. The serum TNF-α level was higher in the poor prognosis group than the levels in the good prognosis group. Moreover, logistic regression analysis revealed that the serum TNF-α level was a risk factor for poor prognosis of patients with SAE. The possible reason is that TNF-α can directly mediate the development of inflammatory response and induce the release of other cytokines, such as interleukin-8 and interleukin-6, leading to a cytokine cascade and the formation of a complex regulatory network. This cascade can initiate systemic inflammatory response syndrome, causing severe inflammatory responses in multiple important organs and inducing multiple organ failure, which in turn worsens the patient's condition and negatively affects prognosis [21, 22].

MCP-1, also known as monocyte chemotactic activating factor and monocyte activating factor, plays an important role in the occurrence and development of hypoxic-ischemic brain injury [23]. In this study, the serum MCP-1 level was positively correlated with the SOFA score of patients with SAE, and it was significantly higher in the poor prognosis group than in the good prognosis group. Furthermore, the serum MCP-1 level is closely associated with the disease severity and prognosis, being consistent with previous literature [24]. MCP-1, mainly produced by monocytes, participates in the migration of neutrophils, natural killer cells, memory T cells, and monocytes. It recruits these cells to inflammatory lesions, aggravating the inflammatory response and leading to inflammatory injury of multiple organs and tissues, thereby worsening the condition of disease and the prognosis [25, 26].

NSE, secreted by neuroendocrine cells, is a protease widely present in human nerve tissues, which can nourish nerves and participate in nerve energy metabolism. In the case of cranial nerve injury, NSE can diffuse into intercellular space and cerebrospinal fluid [27]. NSE is a biochemical marker for brain diseases such as cerebral infarction and brain injury, and an increased serum NSE level usually indicates the worsening of neurological function [28, 29]. In this study, the serum NSE level was significantly correlated with the severity of SAE and could seriously impact the prognosis of patients. In patients with SAE, the systemic inflammatory response can lead to blood-brain barrier damage, making NSE enter the bloodstream from the central nervous system. That leads to abnormal energy metabolism in brain tissues due to NSE deficiency, thus triggering neuronal apoptosis, perivascular edema, central pontine myelinolysis, astrocyte terminal swelling, and multiple necrotic white matter lesions, which can worsen the prognosis of patients [30, 31]. Furthermore, the ROC curves were plotted in this study, and it was found that the area under the ROC curve of serum TNF-α, MCP-1, and NSE levels for predicting the poor prognosis of patients with SAE was > 0.7 for all three biochemical markers, suggesting certain predictive value. The predictive value of the combined detection of these three indicators was higher. Therefore, in the future, close attention should be paid to the serum TNF-α, MCP-1, and NSE levels in patients with sepsis; patients with abnormal levels of the three indicators should be given brain tissue-protecting and cerebral metabolism-improving treatment to prevent the occurrence of SAE or reduce the severity of disease, thereby ameliorating the prognosis of disease outcome in patients.

Conclusion

TNF-α, MCP-1, and NSE levels are closely associated with the severity of SAE and can be used to predict the prognosis of the sepsis outcome. It is necessary to closely monitor the changes in the above three indicators in patients for early evaluation of severity, thereby providing references for the development of timely, adequate therapeutic regimens.

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Conflict of interest

The authors declare no conflict of interest.

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