

# Changes of rScO<sub>2</sub> and ScvO<sub>2</sub> in children with sepsis-related encephalopathy with different prognoses and clinical features

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**Abstract.** Clinical features of sepsis-associated encephalopathy in children with different prognoses were analyzed and the changes of regional cerebral oxygen saturation (rScO<sub>2</sub>) and central venous oxygen saturation (ScvO<sub>2</sub>) were measured. Eighty children with sepsis-related encephalopathy, admitted to the Pediatric Intensive Care Unit (PICU) of the Children's Hospital Affiliated to Zhengzhou University, were enrolled in this study and post-intensive care syndrome (PICS) scoring was performed within 24 h after admission. Patients were separated into groups according to the score results and treatment outcomes. Clinical features, functional tests, imaging examinations, PICS scores, and modified Glasgow Coma Scale (GCS) scores were compared among children with varying severities and prognoses. The changes of rScO<sub>2</sub> and ScvO<sub>2</sub> at different time-points among children with different prognoses were measured and compared. According to PICS scores, there were 8 non-critically ill children, 42 critically ill children, and 30 extremely critically ill children. Fifty-two children survived, and the survival rate was 65%. Comparison of the clinical characteristics of children with different conditions showed that deep coma, generalized seizure, severe electroencephalogram (EEG) abnormalities, and the survival of children were significantly associated with the severity of disease (P<0.05). At the same time, compared to the survivors group, the rates of generalized seizures and severe EEG abnormalities were significantly increased in the deceased children group, while the PICS

and GCS scores were significantly decreased (P<0.05). rScO<sub>2</sub> values in the deceased group were lower than those in the survival group at different time-points, but the differences were not significant (P>0.05). On the contrary, ScvO<sub>2</sub> values were significantly higher in the deceased group than those in the survivors group (P<0.05). The lower the PICS and GCS scores in children with sepsis-related encephalopathy, the more serious the condition, and the more likely to develop disturbance of consciousness, epileptic seizures, and abnormal EEG changes. Whereas, changes of ScvO<sub>2</sub> are closely related to prognosis.

## Introduction

Sepsis, a disease caused by infection in any part of the body, can eventually lead to systemic inflammatory reactions and high morbidity and mortality (1,2). Sepsis-related encephalopathy refers to brain dysfunction caused by sepsis reactions. Sepsis-related encephalopathy is often reversible, and its pathogenesis remains unclear. It is generally believed that sepsis-related encephalopathy is closely related to abnormal neurotransmitters, cerebrovascular dysfunction, and inflammatory injury. In spite of the advanced anti-infective technology and the up-to-date organ support technology, the mortality rate of sepsis is still as high as 3.5%, and the cost of treatment is high, which seriously affects people's life quality (3,4). Therefore, the early diagnosis and treatment of sepsis is particularly important. The key to early detection is the monitoring of the disease status and some important indicators, and the key to treatment is the control of infection. Central venous oxygen saturation (ScvO<sub>2</sub>) can be used for targeted screening of patients with early sepsis (5). In addition, a study has found that regional cerebral oxygen saturation (rScO<sub>2</sub>) is closely related to ScvO<sub>2</sub> (6). The present study included 80 children with sepsis-related encephalopathy who were admitted to the Pediatric Intensive Care Unit (PICU) of the Children's Hospital Affiliated to Zhengzhou University (Zhengzhou, China) from January 2015 to January 2018. Clinical data of the patients were collected and the changes of ScvO<sub>2</sub> and rScO<sub>2</sub> among children with different prognoses were compared.

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*Key words:* sepsis-associated encephalopathy, clinical features, rScO<sub>2</sub>, ScvO<sub>2</sub>, prognosis

## Patients and methods

**Clinical data.** Eighty children with sepsis-related encephalopathy, admitted to the PICU of the Children's Hospital Affiliated to Zhengzhou University from January 2015 to January 2018, were enrolled. Inclusion criteria: patients who met the diagnostic criteria for sepsis in children established by the International Children's Sepsis Conference (7). Patients with sepsis-associated encephalopathy were selected according to their symptoms. Exclusion criteria: patients with central nervous system infection, patients with traumatic brain injury, and patients with uremia encephalopathy and hepatic encephalopathy. The infection sources were located in different parts; there were 28 cases of lung infection, 37 cases of sepsis, 12 cases of intestinal infection, and 3 cases of skin and soft tissue infection. This study was approved by the Ethics Committee of the Children's Hospital Affiliated to Zhengzhou University. Patients who participated in this research had complete clinical data and signed informed consents were obtained from their parents.

**Observation indicators.** Post-intensive care syndrome (PICS) scoring and Glasgow Coma Scale (GCS) scoring were performed on children with sepsis-related encephalopathy within 24 h after admission. According to PICS scores, >80 points was classified as non-critically ill group, 70-80 points was defined as critically ill group, and <70 points was the extremely critically ill group. There were 8 cases in the non-critically ill group, 42 cases in the critically ill group, and 30 cases in the extremely critically ill group. Twelve patients died in the critically ill group and 16 patients died in the extremely critically ill group. Patients were separated into 2 groups according to the treatment outcomes: 52 patients were included in the survivors group and 28 patients in the deceased group. Clinical characteristics of children with different prognoses were observed. Changes of ScvO<sub>2</sub> and rScO<sub>2</sub> were measured at the time of diagnosis (T1), at 24 h (T2) and 48 h (T3) after diagnosis. Near-infrared spectroscopy (NIRS) (INVOS3100; Unity Scientific, Milford, MA, USA) was used to monitor the local rSO<sub>2</sub>, and the rScO<sub>2</sub> was monitored in the forehead of patients. NIRS can be used for non-invasive assessment of rScO<sub>2</sub> through the intact skull in human subjects by detecting the mixed transmission intensity of oxyhemoglobin and reduced hemoglobin. NIRS light penetrates easily the human tissue and can enter a few centimeters into the cranial. Special substances in tissues, such as hemoglobin, myoglobin and cytochrome, have wavelength-dependent absorption characteristics, which have a great influence on the transmitted light and the reflected light intensity. The human brain contains 600-1,000 mg of hemoglobin per 100 g of tissue and is well-suited for monitoring using NIRS. Hemoglobin is the main color base of near-infrared light decay in the brain. When the oxidation state of the body changes, its absorption spectrum changes, resulting in a change in the intensity of the light penetrating the organism. According to this, the oxygenation state of hemoglobin can be detected (8). Dynamic electroencephalogram (EEG) changes were monitored and CT scans were performed after the condition of the patients had improved. Follow-up was continued for 3 months after discharge.

Table I. Baseline characteristics of the patients.

Index	Patients (n=80)
Age (months)	16.5±5.2
Sex	
Male	48
Female	32
State of consciousness	
Lethargy	23
Light coma	27
Deep coma	30
Cases of hyperthermia	42
Seizure situation	
Systemic seizures	42
Localized seizures	38
EEG situation	
Mild to moderate dispersion abnormal number	44
Severe abnormal number	36
Head CT examination	
Mild to moderate abnormality	57
Severe abnormality	23
Scores	
PICS score	71.4±12.6
GCS score	7.1±2.6
Treatment outcomes	
Survivors	52
Deceased	28

EEG, electroencephalogram; PICS, post-intensive care syndrome; GCS, Glasgow Coma Scale.

**Statistical analysis.** SPSS 21.0 statistical software (IBM Corp., Armonk, NY, USA) was used for the statistical analysis of the data. Measurement data were expressed as mean ± standard deviation. Count data were expressed as cases (n). Continuous variables were compared using t-test. Categorical variables were compared using Chi-square test or Fisher's test. ANOVA was performed for the comparison between groups. Least Significant Difference was the post-hoc test used in our study. P<0.05 was considered to indicate a statistically significant difference.

## Results

**Baseline characteristics of the study subjects.** The mean age of the patients was 16.5±5.2 months, and there were 48 male and 32 female patients. All the children had disturbance of consciousness, including 30 cases of deep coma, 27 cases of shallow coma, and 23 cases of drowsiness. Fever was detected in all patients, and there were 42 cases of hyperthermia and 38 cases of non-hyperthermia. Seizures were observed in all patients, and there were 42 cases of systemic seizures and 38 cases of local seizures. EEG was performed

Table II. Comparison of clinical features of children with different conditions.

Groups	Cases	Hyperthermia	Deep coma	Systemic seizures	Severe abnormalities of EEG	Severe abnormalities of head CT	Survival cases
Non-critically ill group	8	4	0	1	1	0	8
Critically ill group	42	21	12	22	16	11	30
Extremely critically ill group	30	17	18	19	19	12	14
$\chi^2$ /Fisher's value		0.409	12.709	6.411	8.085	5.216	9.503
P-value		0.896	0.001	0.038	0.015	0.078	0.009

EEG, electroencephalogram.

Table III. Comparison of clinical features of children with different prognoses.

Groups	Cases	Hyperthermia	Deep coma	Systemic seizures	Severe abnormalities of EEG	Severe abnormalities of head CT	PICS score	GCS score
Survivors group	52	23	16	22	18	11	77.9±8.1	8.3±2.2
Deceased group	28	19	14	20	18	12	59.2±10.4	4.9±1.6
$\chi^2$ /t value		4.074	2.872	6.189	6.474	4.185	8.930	8.145
P-value		0.061	0.146	0.019	0.018	0.068	<0.01	<0.01

EEG, electroencephalogram; PICS, post-intensive care syndrome; GCS, Glasgow Coma Scale.

on the 80 patients, and mild to moderate abnormalities were observed in 44 cases, and severe abnormalities in 36 cases. All patients underwent cranial CT examination. The initial manifestations were diffuse edema of whole brain symmetry, or low density changes and necrosis of the fronto-temporal part, while late manifestations were cranial sulcus enlargement and ventricles enlargement. The number of patients with mild to moderate head CT abnormalities was 57, and the number of patients with severe abnormalities was 23. Final treatment outcomes for all patients were 52 survivors and 28 deceased children (Table I).

*Comparison of clinical features of children with different conditions.* PICS scoring was performed on children with sepsis-related encephalopathy immediately after admission. There were 8 cases in the non-critically ill group, 42 cases in the critically ill group, and 30 cases in the extremely critically ill group. Statistical analysis showed that there were no statistically significant differences in hyperthermia and severe brain CT abnormalities among the groups of patients with different disease conditions ( $P>0.05$ ). There were statistically significant differences among the 3 groups regarding deep coma, systemic seizures, severe EEG abnormalities and the survival of the children ( $P<0.05$ ). The clinical characteristics of children with different conditions are shown in Table II.

*Comparison of clinical features of children with different prognoses.* Patients were separated into 2 groups according to

the treatment outcomes: 52 patients in the survivors group and 28 patients in the deceased group. Statistical analysis showed that hyperthermia, severe abnormalities of head CT and deep coma were not associated with patients' survival ( $P>0.05$ ). Systemic seizures, severe EEG abnormalities, PICS scores and GCS scores were significantly associated with the prognosis of patients ( $P<0.05$ ) (Table III).

*Comparison of rScO<sub>2</sub> and ScvO<sub>2</sub> in children with different prognoses.* The clinical characteristics of children with different prognoses were observed. Changes of ScvO<sub>2</sub> and rScO<sub>2</sub> at T1, T2 and T3 were measured. Results showed that rScO<sub>2</sub> values in the deceased group were significantly lower than those in the survivors group at the different time-points, but the differences were not significant ( $P>0.05$ ). On the contrary, ScvO<sub>2</sub> values were significantly higher in the deceased group than in the survivors group, and the differences were statistically significant ( $P<0.05$ ). There was no statistically significant difference in the changes of rScO<sub>2</sub> and ScvO<sub>2</sub> at the different time-points in the same group ( $P>0.05$ ). Post-hoc test was used to compare the changes of rScO<sub>2</sub> and ScvO<sub>2</sub> at two different time-points, and the results showed that the differences were not statistically significant ( $P>0.05$ ) (Table IV).

*Treatment and follow-up results.* After active rescue, some patients' consciousness gradually recovered, including recovery in <24 h in 5 cases, 24-72 h in 12 cases, >72 h to 1 week

Table IV. Comparison of rScO<sub>2</sub> and ScvO<sub>2</sub> in children with different prognoses.

Groups	Cases	T1		T2		T3	
		rScO <sub>2</sub>	ScvO <sub>2</sub>	rScO <sub>2</sub>	ScvO <sub>2</sub>	rScO <sub>2</sub>	ScvO <sub>2</sub>
Survivors group	52	63.6±10.9	70.9±9.8	62.3±11.3	72.1±9.1	60.3±11.0	69.2±11.9
Deceased group	28	59.3±10.5	76.3±10.2	59.6±10.9	76.5±10.0	58.7±9.2	75.2±8.5
t value		1.679	-2.320	1.019	-1.998	0.637	-2.584
P-value		0.097	0.023	0.311	0.049	0.526	0.012

rScO<sub>2</sub>, regional cerebral oxygen saturation; ScvO<sub>2</sub>, central venous oxygen saturation.

in 34 cases, and >1 week in 1 case. Seizure symptoms in children treated with antiepilepticism were gradually controlled within 1 week. At the time of discharge, there were 37 cases of normal neurological function and 15 cases of abnormal neurological function. Among them, there were 2 cases of mild hearing impairment, 3 cases of mild exercise retardation, and 2 cases of mild decrease of muscle tension. The 3 months follow-up in the 52 cases of the surviving children showed that the neurological functions were completely recovered. Cranial image (CT or MRI) was normal in 45 cases, and abnormal in 7 cases. The 7 abnormal cases manifested as the widening of sulcus and a sign of brain atrophy with enlarged ventricles. EEG was performed on all 52 cases during follow-up, and 38 cases were normal, while 14 cases were mildly abnormal.

## Discussion

Sepsis-related encephalopathy refers to the central nervous system dysfunction caused by sepsis, with no effective treatment, and Papadopoulos *et al* have pointed out that the incidence of septic brain disease was 8-70% (9). Wilson and Young (10) redefined the brain dysfunction caused by sepsis as septic-related encephalopathy, which was a very common disease in PICU with a high mortality rate and high hospitalization cost, that was often seen in children. Pathogenesis of septic encephalopathy remains unclear. At present, it is believed that the pathogenesis of septic encephalopathy mainly includes inflammatory mediator release, impaired blood-brain barrier, mitochondrial dysfunction, neurotransmitter changes and cell apoptosis. Terborg *et al* (11) have pointed out that vasomotor dysfunction which was regarded as the main cause of sepsis-associated encephalopathy, often leads to dysregulation of cerebral blood flow and can directly affect brain function and cerebral blood circulation. Studies have shown that patients with sepsis have relatively high levels of aromatic amino acids in plasma, which can easily lead to the production of pseudo-neurotransmitters, affect neuronal function, and cause symptoms and signs of various neurological impairments including disturbance of consciousness (12,13). Sharshar *et al* (14) performed pathological examination on the brain tissue of patients who died of sepsis and found that the incidence of microabscess was high and microabscess may be one of the causes of sepsis-associated encephalopathy. In addition, many substances, such as IL,

TNF, Glu, and NO can act on the nervous system in different ways, causing corresponding damage to the nervous system. Moreover, improper use of drugs and infusion can also induce iatrogenic brain injury.

The high incidence and mortality of sepsis-associated encephalopathy have attracted closer attention from scholars. In sepsis-associated encephalopathy is the sepsis complication which increases mortality. Eidelman *et al* (15) comprehensively elaborated and analyzed the definition, etiology and mortality of sepsis-associated encephalopathy and found that the mortality of septic encephalopathy was 33-39%. At present, APACHE II scoring system is generally used in ICU to assess the severity of illness of adult patients. PICS scoring system is used for the assessment of pediatric patients because of their special characteristics. PICS scores include multiple indicators, such as vital signs, pH, electrolytes, renal function, and gastrointestinal function. However, PICS scoring does not include neurological assessment. GCS score can supplement and improve the PICS score to some extent. Therefore, this study combined the two scoring systems to assess the disease condition. In this study 80 children admitted to the Children's Hospital Affiliated to Zhengzhou University with sepsis-associated encephalopathy were assigned. The final treatment outcomes were 52 survivors and 28 deceased, with a survival rate of 65%. PICS scoring was performed on children with sepsis-related encephalopathy immediately after admission and patients were separated into different groups according to their scores. It was observed that deep coma, general seizures, severe EEG abnormalities, and the survival of children were significantly associated with the severity of the disease. Therefore, we can assess patient's condition by observing patient's state of consciousness, epileptic seizures and EEG changes. Children were separated into the survivors and the deceased groups according to the treatment outcomes. The systemic seizures, severe EEG abnormalities, PICS and GCS scores were significantly associated with the prognosis of patients. Therefore, patient's prognosis can be assessed through seizures and EEG changes in the patients. PICS and GCS scores are important for evaluating the prognosis of children. The lower the PICS score, the more severe the clinical manifestations of the disease in children, and the higher the mortality rate. Therefore, PICS and GCS scores are of great significance in assessing the severity of critically ill children.

The current treatment for sepsis patients is mainly early recovery, control of the source of infection and empirical

anti-infective treatment. Pathological changes in sepsis are often manifested as cellular hypoxia caused by vascular reactivity. Therefore, maintaining hemodynamic stability is crucial for children with sepsis. Under stable respiratory conditions, ScvO<sub>2</sub> can reflect the body's oxygen supply and demand balance. By assessing tissue oxygenation in children with septic-associated encephalopathy, NIRS can monitor rScO<sub>2</sub> changes, and to some extent reflect the changes in brain metabolism. A study of 60 patients with septic shock has shown that early monitoring of patient's ScvO<sub>2</sub> to guide the fluid resuscitation of septic shock can effectively reduce the incidence and mortality of multiple organ dysfunction syndrome, which is conducive of improving the prognosis of patients (16). In the present study, changes of ScvO<sub>2</sub> and rScO<sub>2</sub> were measured at the T1, T2 and T3 time-points. The results revealed that the ScvO<sub>2</sub> values in the deceased group were significantly higher than those in the survivors group, at all different time-points, and the differences were statistically significant, suggesting that changes in ScvO<sub>2</sub> are closely related to the prognosis of children. The treatment of children with septic-related encephalopathy can be assisted by continuous monitoring of ScvO<sub>2</sub>. It is beneficial to the prognosis of children and is worthy of clinical application.

At present, EEG is widely used in the diagnosis of patients with sepsis-associated encephalopathy, and the sensitivity is high (17). Although some patients with septic brain disease have no nervous system dysfunction, the mild diffuse abnormal waveform can usually be observed through EEG. In this study, electroencephalography was performed on all 80 cases and 44 patients showed mild to moderate abnormalities, 36 patients showed severe abnormalities, and of the 28 deceased cases, 18 had severe abnormalities of EEG, indicating that the prognosis of patients with septic-related encephalopathy is significantly related to changes in EEG. During follow-up, the conditions improved in some patients. However, there were still some children with abnormal EEG. Therefore, EEG is of great significance for the evaluation of sepsis-associated encephalopathy. EEG can help not only the early diagnosis of children but also the assessment of the condition and prognosis during treatment. CT can show any changes in the head of children with sepsis, such as narrowing of the ventricle, sulci, and cisterna, unclear gray matter, local low-density shadow or even severe liquefaction necrosis. In the recovery period, the head CT showed mild to moderate brain atrophy. In this study, in the early stages of the disease, the head CT showed diffuse edema of the whole brain, that is, narrowing of the sulci, ventricles, cisterns, or unclear boundaries of gray matter. It was found that during the recovery and 3 months follow-up most patients returned to normal, but some children still showed signs of brain atrophy with widening of the sulcus and ventricles. The results of this study indicate that head CT can be used to assess brain damage, assist clinical treatment and evaluate the prognosis. Patients with sepsis-associated encephalopathy generally have severe symptoms, high mortality and poor prognosis. For surviving patients, nervous system damage can be gradually repaired. In this study, the consciousness in the majority of the children was gradually recovered within 1 week. The convulsive symptoms of the children treated with antiepileptic therapy were gradually controlled within 1 week. After 3 months of follow-up, the neurological examination showed

that the nervous system of all the surviving children returned to normal, suggesting that there is still a lot of room for the neurological rehabilitation of sepsis related encephalopathy if the children can survive the acute stage safely. However, this study has some limitations. Firstly, this study is a retrospective study. Exclusion diagnosis was adopted for the diagnosis of sepsis-related encephalopathy. If we could prospectively use EEG, somatosensory evoked potentials combined with imaging to diagnose sepsis-related encephalopathy, the incidence statistics could be more accurate. Secondly, this study is a single-center survey. The sample size collected in a short time is relatively small, and the conclusions obtained cannot fully reflect the overall level of China. As a result, a large-scale multi-center epidemiological survey is needed.

Collectively, this study shows that the lower the PICS and GCS scores of children with sepsis-related encephalopathy are, the more severe the disease is, and the more likely they are to suffer from consciousness disorder, epileptic seizure and abnormal EEG changes. The change of ScvO<sub>2</sub> is closely related to the prognosis of children. Therefore, for children with sepsis-related encephalopathy, continuous monitoring of their consciousness, seizures, EEG and ScvO<sub>2</sub> changes can be used to evaluate the treatment status and prognosis of children, which is worthy of clinical promotion.

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#### Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

#### Authors' contributions

JG conceived and designed this study. YC, QW and JS acquired and analyzed the data. LC and ZJ were involved in the design of the study, drafted, revised and finalized the manuscript. All authors read and approved the final manuscript.

#### Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Children's Hospital Affiliated to Zhengzhou University (Zhengzhou, China). Patients who participated in this research had complete clinical data and signed informed consents were obtained from their parents.

#### Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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