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# Combined BIS and Serum Neuron Specific Enolase in the predictive value of cardiopulmonary resuscitation patients.

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***Abstract:***
***Objective*** *To evaluate the prognostic value of the bispectral index (BIS)and neuron-specific enolase (NSE) in patient with cardiopulmonary resuscitationpatients.*
***Methods*** *Forty-four patients with restoration of spontaneous circulation (ROSC) after CPR were treated with MTH. The BIS values were recorded and the serum NSE was measured at: 24 h, 48 h, and 72 hours respectively after ICU admission. Neurological outcome was classified according to the Pittsburgh cerebral performance category (CPC 1 to 5) at 3 months after ICU discharge.*
***Results*** *Thirteen patients had agood neurological outcome with CPC score 1-3, and thirty-one patients had apoor neurological outcome with CPC 4-5 at 3 months. Compared with good prognosis group, the NSE values were significantly higher in the poor prognosis group on day 2 and day 3 after admission [48 h:( 77.0±11.4) vs. Cpc4-5: (38.2±23.9)ng/mL ; 72 h:(87.0±9.3) vs. Cpc4-5: (45.8±26.4)ng/mL,P＜0.05. NSE increased in the poor neurological outcome group at 48h and 72h, and decreased significantly in the good group at the same time[△NSE 24 h-48 h : (37.3±28.7)ng/mL vs.(-10.2±12.1)ng/mL ; △NSE 48 h-72h : (5.4±13.2) ng/mL vs. (-4.3±4.2 ng/mL), P<0.05]. Over the 72hof monitoring, the mean BIS values were lower in the poor prognosis group compared to the good prognosis group at 48 h [(39.2±24.1) vs. (78.0±12.4);72 h; (45.7±26.4) vs. (89.0±7.3), P＜0.05.*
***Conclusions*** *The values of BIS and NSE were effective prognostic indicators for the neurological outcome of patients with MTH after CPR.*
***Keywords****: Neuron-specific enolase,Bispectral index, mild therapeutic hypothermia, cardiopulmonaryresuscitation, Neurologic outcome, Return of spontaneous circulation.*

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## I. Introduction:

One of the main signs of success in cardiopulmonary resuscitation is voluntary circulatory recovery or restoration of spontaneous circulation (ROSC), but ROSC is only the basic requirement of the rescue process for cardiac arrest patients, and the rehabilitation of neurological function is the ultimate goal of cardiopulmonary resuscitation. The Treatment of hypothermia has been shown to improve prognosis in patients with cardiac arrest coma [1, 2, 3, 4, 5], to assess the prognosis of these patients to provide an important decision making on the basisof clinically. Commonly used evaluation means such as GCS score, EEG, somatosensory evoked potentials, imaging examination, some indicators are more subjective, some of the detection methods are complex, the repeatability is poor, clinical application is limited. Neuron-specific enolase can be used to predict the neurological prognosis of patients with coma after successful cardiopulmonary resuscitation [6, 7, 8]; EEG dual-band index monitoring was initially used to monitor the depth of anaesthesia in patients with general anaesthesia, and is also currently being applied to clinical monitoring of patient'sconsciousness state and neurological impairment levels [9,10], and the indicator quantification, can be continuously monitored by the bedside.

Neuron-specific enolase (NSE) is a known marker of ischemic brain damage and has already been evaluated in traumatic brain injury [10], stroke [11] and anoxic encephalopathy after cardiac arrest [12,13]. NSE, the neuronal form of the glycolytic enzyme enolase, is found almost exclusively in neurons and cells of neuroendocrine origin. It is a dimeric form com- pounded of two $\gamma$ subunits that converts 2-phosphoglycerate into phosphoenolpyruvate, measurable in blood and cerebrospinal fluid [14].

Bispectral Index Scale (BIS) a parameter derived from a mathematical analysis of the EEG, depicts brain activity. BIS values range from 0 to 100: 100 indicates a fully awake adult and 0, total electrical silence of the brain.BIS values between 40 and 60 are considered to be indicators of adequate sedation.Although BIS was

first introduced as a tool to monitor anaesthesia in the operating room (OR), its use has been extended to assess sedation outside the OR, for example in the ICU or the emergency department. [5] Moreover, it has been suggested that there might be a good correlation between neurological status and BIS among patients with ischemic or traumatic brain injury. In addition, it has been implied that in these clinical settings, BIS could serve as a good predictor of outcome [11,12].

In this study, the relationship between neural functional prognosis and neuron-specific enolase and EEG dual-frequency index was investigated in patients with cardiac arrest coma treated with hypothermia.

## II. Method and Materials:

**2.1 General Information-**Selected 44 patients from March 2014 to March 2017in emergency rescue room, ICU admitted after cardiac arrest resuscitation ROSC and coma Patients, to rule out cardiac arrest before the serious chronic heart, lung, brain and other organ diseases. Among them, 28male patients, 16 female patients, age 19 ~ 82 years old, (65.0±16.5) years old; 10patients of sudden cardiac arrest in hospital circumcentre and 34patientscardiac arrest in hospital. The Causes of cardiac arrest are acute myocardial infarction in 17 cases, cardiomyopathy in 2 cases, malignant arrhythmia in 5 cases, septic shock in 2 cases, asphyxia in 5 cases, pulmonary embolism in 6 cases, respiratory failure in 5 cases.

**2.2 Research methods-** Patients in ROSC immediately after the infusion of 4 ℃ frozen saline ml/kg at the same time using a cooling blanket (hico-hypotherm 680 type cooling Blanket, Germany) for the whole-body cooling, cooling speed 0.5~1.0℃/h, so that the anus temperature to 32~34℃, maintain the sub-low temperature. Midazolam, propofol and fentanyl were used in low-temperature process, and Ramson scored. After 1 h, the body temperature was gradually recovered to 37~37.5℃ at 0.25℃/h speed, and the sedative drug was started when the body temperature recovered to 37 ℃. The ROSC standard is can touch the pulse or the blood pressure and maintain more than s, can be accompanied by a sigh like breathing. The success criteria for CPR were Rosc to maintain more than 1H [16]. After collecting ROSC 24hr, 48hr, 3 ML of peripheral venous blood (4,3 r/min centrifugation 5~ min) separating plasma, taking serum to detect NSE, using Roche cobasautomatic electrochemical chemiluminescence Immunoassay (Switzerland) to detect serum NSE. After ROSC, the patient was monitored by the BIS monitoring module of Philip Monitor, and the BIS value was recorded in 24hr, 48hr and three time-points respectively. Neurological function evaluation using cerebral performance categories (CPC) score, mental recovery or the loss of moderate to severe neurological function was cpc1~3 for good prognosis;coma or death is Cpc 4~5 score for poor prognosis [3, 4].

Bispectral index monitoring was performed for all patients at the time of admission to the ICU. After skin preparation with alcohol, the sensor with four electrodes was positioned diagonally on the forehead. The first electrode was placed at the centre of the forehead, approximately 2 in. above the bridge of the nose. The second electrode was placed just laterally and inferiorly to the first one. The third electrode was placed on the temple, between corner of the eye and hairline. The fourth electrode was directly placed above the eyebrow. The sensor was connected to a Philips Intellivue MP50 BIS monitor (Philips MedizinSystem, Boeblingen, Germany). No patient received any sedative before or during BIS monitoring. Artifacts in the BIS caused by physical examination and care of the patient were removed during analysis. Continuous BIS monitoring was performed for 12 h, and BIS values were recorded every 30 min. For each recording, BIS values with a signal quality index (SQI) greater than 80 and electromyographic (EMG) artefacts less than 45 were used to calculate the average BIS score. Data were excluded if they were (1) contaminated by gross artefacts, such as eye movements, (2) contaminated by major EMG activity (EMG > 45), and (3) the SQI was <80. Serum NSE and S100 protein levels were assayed three times during the first 3 days using immunoluminometric assays, and the maximum levels of NSE and BIS wereanalyzed.

**2.3 Statistical Analysis-** Using SPSS 16.0 statistical software processing data, measurement data with mean ± standard deviation (x±s), the comparison between groups using variance analysis, the rate of comparison use Fisher accurate probability method, NSE level and BIS value of the diagnostic effectiveness and limit values using ROC curve Analysis, and calculate the area under the curve. The difference of $P < 0.05$ was statistically significant.

## III. Results:

Patient data (shown in table 1): The prognosis of the group (cpc1-3) Age (52±20.4) is lower than the poor prognosis Group (cpc4-5) (P<0.05), the difference between the two groups of sex ratio is not statistically significant. There was no statistically significant difference in body temperature during sub-hypothermia in both groups. NSE Value (shown in table 2), There was no significant change between the two groups after ROSC [(cpc1-3: (43.9±25.9) vs. Cpc4-5: (52.8±34.8)), after ROSC24H, the prognosis of a good group of NSE significantly decreased (*P*<0.05) [(Cpc1-3: (33.2±17.5 vs. Cpc4-5: (90.1±42.7)), after Rosc, the prognosis of a good group of NSE level is also lower than the prognosis of the poor group (*P*<0.05) [(Cpc1-3: (29.2±17.0 vs. cpc4-5 37.0)). After Rosc h (Fig. 1), the cut-off value of NSE 40.3 ng/ml, sensitivity 79%, specificity 99%. In72 H, NSE valueswere 36.6 ng/ml, the sensitivity degree is 86%, the specificity is 100%.

**Table 1.** General Data of the two groups

(*X*±*S*)

| INDEX | Number of patients (44) | CPC1-3(13) | CPC4-5(31) | *P* Value |
|---|---|---|---|---|
| AGE | 62.2±15.5 | 52±20.4 | 67±10.9 | <0.05 |
| GENDER (MALE) | 28/44 | 8/13 | 21/31 | >0.05 |
| HOSPITAL CIRCUMCENTER ARREST | 10/44 | 4/13 | 7/31 | >0.05 |
| CAUSES OF CARDIAC ARREST | | | | |
| ACUTE MYOCARDIAL INFACTION | 17/44 | 5/13 | 13/31 | >0.05 |
| MYOCARDIAL DISEASE | 2/44 | 0/13 | 2/31 | >0.05 |
| MALIGNANT HEART RHYTHM DISORDER | 5/44 | 3/13 | 2/31 | >0.05 |
| SEPTIC SHOCK | 2/44 | 1/13 | 1/31 | >0.05 |
| RESPIRATORY FAILURE | 8/44 | 2/13 | 6/31 | >0.05 |
| PULMONARY EMBOLISM | 6/44 | 1/13 | 5/31 | >0.05 |
| ASHPHYXIA | 5/44 | 2/13 | 3/31 | >0.05 |

NOTE- GOOD PROGNOSIS CPC1-3, POOR PROGNOSIS -CPC4-5, CPC (CEREBRAL PERFORMANCE CATEGORIES)

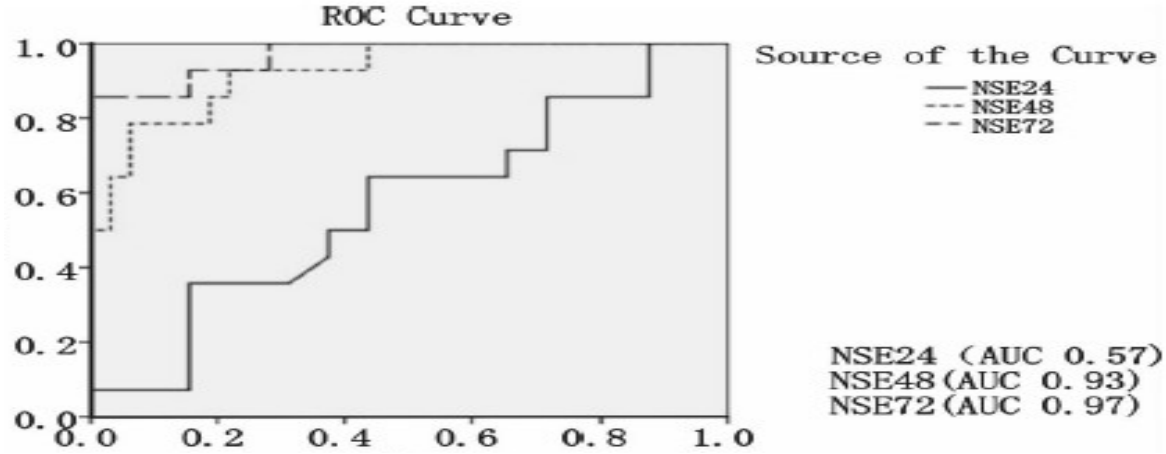
**Table2.** 24,48,72h BIS and NSE level of two groups

(*X*±*S*)

| INDEX | BIS (24 h) | BIS (48 h) | BIS (72 h) | NSE (24 h) | NSE (48 h) | NSE (72 h) |
|---|---|---|---|---|---|---|
| CPC1-3(13) | 25.0±9.2 | 77.0±11.4 | 87.0±9.3 | 43.9±25.9 | 31.2±17.4 | 27.2±18.0 |
| 95% *CI* | 19.6～29.8 | 69.8～84.2 | 84.8～92.2 | 23.9～54.8 | 23.1～43.1 | 19.3～39.0 |
| CPC4-5(31) | 21.3±12.4 | 38.2±23.3 | 45.8±26.4 | 52.8±34.8 | 90.2±42.3 | 95.4±37.5 |
| 95% *CI* | 18.9～26.1 | 30.6～47.7 | 35.2～54.2 | 40.3～65.4 | 73.7～103.5 | 82.0～107.2 |
| *P*VALUE | >0.05 | <0.01 | <0.01 | >0.05 | <0.01 | <0.05 |

NOTE：NSE UNIT=NG/ML

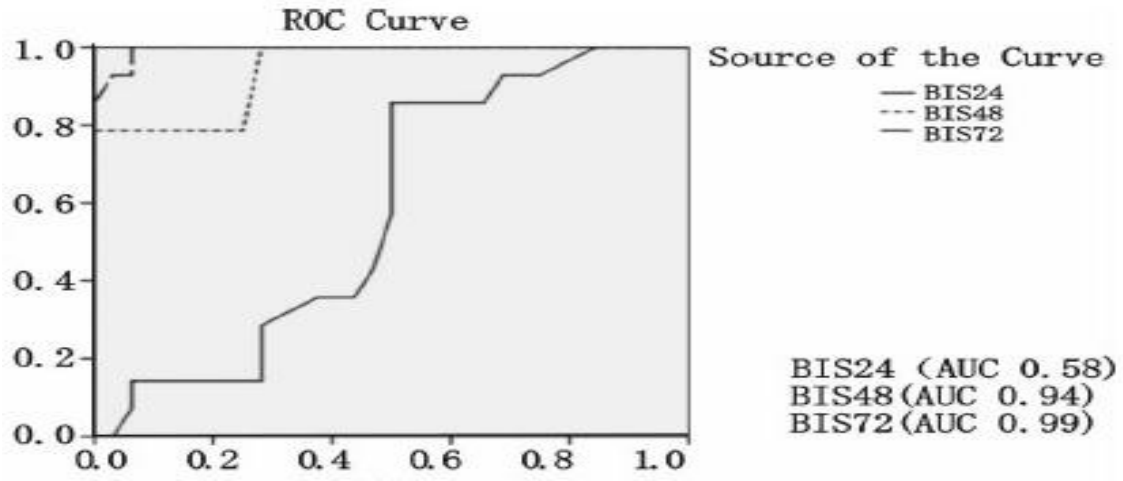
**Fig. 1.**The ROC Analysis of the 24，48，72 h NSE level




BIS Value ( shown in table 2): The values of 24, 48 and 72hBIS were recorded in two groups of patients after ROSC,there was no statistically significant difference in the 24hBIS value of both groups [(Cpc1-3: (25.0±9.2) vs. Cpc4-5: (21.3±12.4)),the BIS value at 48 h of good prognosis group was lower than bad prognosis group [(cpc1-3: (77.0±11.4) vs. Cpc4-5: (38.2±23.9))is significantly Higher (*P*<0.05), and the BIS

value at 72h in good prognosis group was significantly higher than bad prognosis group [cpc1-3: 87.0±9.3] vs. Cpc4-5: (45.8±26.4)] ($P$<0.05). The BIS Value at 48h were 69, sensitivity 78.6%, specificity 100%.Whereas at 72H,BIS valueswere 70.5, the sensitivity 100% and the specificity is 99.4% (shown in fig. 2).

**Fig.2**. The ROC Analysis of the 24，48，72h BIS




In the Good Prognosis Group (table 3) The NSE value decreased significantly in both 48H and 72H and the prognosis of the group was lower in the 48th hour than 24 hours, NSE decreased (10.2±12.1) ng/ml, 72nd hour was lower than 48th hour (4.3±4.5) ng/ml. The value of NSE in the poor prognosis group showed an upward trend in the 48th and 72nd hours, especially in the patients with poor prognosis, the 48 H increased significantly in the 24H.The difference of NSE in two groups was statistically significant.

**Table.3.** NSE value difference in both groups.

| **(*X*±*S*)** | | | |
|---|---|---|---|
| **NSE** | CPC1-3 | CPC4-5 | *P* Value |
| **△NSE 24H～48H** | -10.2±12.1 | 36±28.7 | <0.01 |
| **△NSE 48H～72H** | -4.3±4.2 | 5.4±13.2 | <0.05 |
| **NOTE：NSE UNIT- NG/ML** | | | |

## IV. Discussion:

With the development and popularization of the modern cardiopulmonary resuscitation technology, the ROSC rate of patients with cardiac arrest was significantly increased [11], both in hospital and in hospital, but the overall prognosis of patients after ROSC was still not improved significantly. Clinical and experimental studies have confirmed that sub-hypothermia therapy can improve the recovery of neurological function and prognosis of patients after cardiac arrest resuscitation, reducing the case fatality rate [2,9,12]. How to evaluate the prognosis of ROSC patients and improve the scientific basis for clinical decision-making has become an urgent concern for clinicians. Early predictive indicators of neurological function recovery have become an important part of management after cardiac arrest. At present, the commonly used detection methods are neurological clinical evaluation, EEG, somatosensory evoked potentials, neuroimaging and so on, but often there are not timely, interference factors, bedside examination difficulties and other shortcomings, it is possible to find some serum biomarkers combined with a continuous test method at the bedside to determine the neurological function prognosis of ROSC patients earlier is the objective of this study.

NSE is a two-dimer isozyme of Enolase, which is in the neuronal and neuroendocrine cell cytoplasm, and if the neurons are necrotic, the NSE will leak out to the cells, and the concentration of body fluid can be increased. Several studies have confirmed that NSE can be used to predict the prognosis of neurological function after cardiopulmonary resuscitation [8,11,13], the most important advantage of biomarkers is that their levels are not disturbed by sedation or neuromuscular blockers, and can usually be applied in the 1th to several days after cardiac arrest. The results showed that the 48h and 72hNSE levels in the patients with good prognosis were significantly lower than those with poor prognosis, and the NES cut-off values calculated in this study were 79%, 99% in the sensitivity of 40.3 ng/ml. When the NSE value 36.6 ng/ml, the sensitivity degree is 86%, the specificity is 100%. In the good prognosis group, the value of 24 h~48 h and 48h~72h NSE was also lower than that of the poor prognosis group. This study suggests that serum NSE level and its change value can be

used as an important index for the prognosis of neurological function in patients after cardiopulmonary resuscitation and sub-hypothermia treatment.

BISis the power and frequency of the EEG by two-frequency analysis of a numerical value, with 0~100 points, can be used to determine the patient's consciousness state and sedation depth of a common clinical indicators.There are animal experiments found in the occurrence of diffuse brain injury in the pig, the BIS can appear in 24h is worth significantly reduced [14]. Nebout et [12] found that BIS values correlated with the degree of low cerebral perfusion in clinical patients. The BIS monitoring of patients with acute brain injury caused by different aetiology also found that BIS<60 could be used as an indicator of poor prognosis. BIS monitoring was used in patients with Riker after resuscitation of cardiac arrest, and the BIS value of early awake patients was found to be significantly higher. BIS values can be used as predictors of neurological function recovery in patients after cardiac arrest [15,16,17]. BIS value is an effective index to evaluate the degree of coma after cardiopulmonary resuscitation and to determine the prognosis of neurological function, and in the determination of prognosis, combine use of BIS and blood NSE are better than some subjective indicators (such as GCS score, etc.). This study found that there was no significant difference between the 24hBIS value two groups after ROSC in patients with cardiac arrest, which may be related to the use of sedative drugs during the treatment of mild hypothermia. The BIS value of 48 and 72h after ROSC was significantly higher in the prognosis group than in the poor prognosis group, and was significantly correlated with the degree of neurological functional recovery. At the same time, BIS monitoring can be carried out in the patient's bedside, the index quantification, indicating that the BIS value can be used as a more practical and more convenient index for the evaluation of neurological function after cardiopulmonary resuscitation.

## V. Conclusion:

This study suggested that combine use of serum NSE levels and BIS monitoring could be used to evaluate the neurological prognosis of patients with cardiac arrest with sub-hypothermia therapy and to help with clinical decision-making. However, this study is a single-centre clinical study, the sample size is small, and its conclusion needs to be clarified by further evidence-based medicine.

**Conflict of interest**

On behalf of all authors, the corresponding author states that there is no conflict of interest regarding this study.

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