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ORIGINAL ARTICLE

Bispectral index predicts deaths within 2 weeks in coma patients, a better predictor than serum neuron-specific enolase or S100 protein

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Abstract
Purpose We assessed the ability of bispectral index (BIS) to predict clinical outcome (dead or alive within 2 weeks).
Methods In total, 90 coma patients with severe brain injuries underwent BIS monitoring, and serum neuron-specific enolase (NSE) and S100 protein levels were assayed within the first 3 days of admission. Receiver operator characteristic (ROC) curve analysis was used to assess the performance of BIS values for predicting death within 2 weeks. A cutoff value was calculated using the Youden index.
Results A significant negative correlation was found between BIS value and serum NSE and S100 levels. The area under the curve for BIS value was 0.841 ($p < 0.001$, 95 % CI = 0.751–0.931), and higher than for NSE (0.713) ($p = 0.002$, 95 % CI = 0.582–0.844) or S100 (0.790) ($p < 0.001$, 95 % CI = 0.680–0.899). The optimal cutoff of BIS was 32.5. Serum NSE and S100 protein levels and the mortality rate were significantly lower in patients with a BIS value >32.5 than in patients with a BIS value ≤32.5.
Conclusions Bispectral index values may reflect degree of brain injury, and BIS is an objective and noninvasive monitoring method for helping clinicians to predict death in patients with a BIS value ≤32.5.

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Keywords Bispectral index · Neuron-specific enolase · S100 protein · Severe brain injury

Introduction

Coma is a state of profound unconsciousness in which the patient cannot be awakened, fails to respond to external stimuli, and does not show voluntary motor activity. Coma is the result of damage to the brain that may be caused by severe brain injury, such as head injury, cerebral hemorrhage, cerebral infarction, and hypoxic ischemic encephalopathy (HIE) after cardiac arrest. Coma patients with severe brain injuries are treated in the intensive care unit (ICU) and often have poor ICU outcomes, such as persistent vegetative states (VSs) and death within a short time [1]. Thus, it is important to be able to predict outcomes in coma patients with severe brain injuries. However, to date, no good prognostic indictor has been established.

Serum levels of neuron-specific enolase (NSE) and S100 protein, released into the blood after brain injury, have been used in the clinic to predict neurological outcomes after brain injuries [2–4]. Several studies have shown that the NSE and S100 proteins are sensitive and specific markers of brain injury, and these are considered to be promising candidate neurological prognostic predictors in patients with brain injuries [5–7]. However, Moritz et al. [8] reported that serum NSE was less accurate for the prognosis of clinical outcomes in patients with spontaneous subarachnoid hemorrhage than serum SB100. Olivecrona et al. [9] showed that NSE and S100 proteins were poor outcome predictors in patients with severe traumatic brain injury treated by an intracranial pressure-targeted therapy. The difference in NSE and S100 for predicting clinical outcomes among these studies

may be largely the result of the different populations of patients with different causes of brain injury. Thus, additional measures are needed to achieve more accurate predictions of clinical outcomes in patients with various causes of brain injury.

The bispectral index (BIS), a processed electroencephalographic measure, was originally designed as a measure of the depth of anesthesia, and was later used in the ICU to control depth of sedation in patients [10, 11]. BIS values have been reported to be associated with brain injury, Glasgow Coma Score (GCS), and intracranial pressure [12–14]. Higher BIS values are associated with better neurological outcomes in patients with severe brain injuries [15] and in unsedated critically ill patients [16]. Additionally, Schnakers et al. [17] reported that BIS values could distinguish a vegetative state from a minimally conscious state, and were higher in coma patients who recovered after 1 year than those who did not recover. However, Stammet et al. [18] showed no correlation with good outcome for BIS values higher than zero. These differences may be caused by the lack of an established cutoff BIS value for predicting good outcomes.

In this study, we measured BIS values and serum NSE and S100 protein levels in 90 coma patients with various causes of severe brain injury. Serum NSE and S100 protein levels were used to reflect and predict the status of brain injury. The purpose of this study was to assess the ability of BIS to predict clinical outcomes (dead or alive within 2 weeks), and to establish a cutoff BIS value.

Methods

Patients

This prospective study was approved by the Ethics Committees of Hospital No. 401 of the Chinese People's Liberation Army. Because all patients were unconscious and critically ill, a waiver of informed consent was granted.

All patients received similar treatments for brain protection, such as mild hypothermia therapy (body temperature, 33 °–35 °C) and control of intracranial pressure using 20 % mannitol (125–250 ml each time, 2–3 times a day). This study included 90 coma patients with severe brain injuries. Coma patients were excluded if the coma was caused by severe cardiac, respiratory, or renal disease, or drug or metabolic intoxication. Patients who died of extracerebral lesions or received sedatives or muscular relaxants were also excluded. Information on each patient's outcome (dead or alive) was recorded at the end of 2 weeks.

Bispectral index monitoring

Bispectral index monitoring was performed for all patients at the time of admission to the ICU. After skin preparation with alcohol, the sensor (Aspect Medical Systems, USA) with four electrodes was positioned diagonally on the forehead. The first electrode was placed at the center 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 Medizin Systeme, 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) artifacts less than 45 were used to calculate the average BIS score. Data were excluded if they were (1) contaminated by gross artifacts, 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 S100 proteins were analyzed.

Statistical analysis

The data were not normally distributed and are presented as medians and interquartile ranges. Spearman's correlation test was used to examine the correlation between BIS values and NSE and S100 protein levels. A receiver operating characteristic (ROC) curve was used to assess the discriminating performance of BIS, NSE, and S100 to predict death within 2 weeks in coma patients with brain injuries, and the cutoff values for BIS with sensitivity, specificity, positive predictive value, and negative predictive value were calculated using the Youden index. The differences among groups were analyzed statistically using the Kruskal–Wallis analysis of variance. Categorical data were compared with chi-squared tests. Two-way analysis of variance (ANOVA) was used to test the effect of the patient's age on prediction of death within 2 weeks by BIS. Differences in serum NSE and S100 protein levels between the two groups, grouped according to BIS cutoff value, were analyzed using a Mann–Whitney U test. A $p < 0.05$ was considered to indicate statistical significance.

Results

In total, 90 coma patients were grouped according to the cause of their brain injuries: cerebral hemorrhage ($n = 15$), brainstem hemorrhage ($n = 9$), subarachnoid hemorrhage ($n = 8$), cerebral infarction ($n = 12$), hypoxic-ischemic encephalopathy (HIE) after cardiac arrest ($n = 28$), cerebral anoxia after shock ($n = 8$), and head injury ($n = 10$). Table 1 shows the BIS values and the NSE and S100 protein levels in the patients. Patient age, Glasgow Coma Scale (GCS) scores, APACHE (Acute Physiology and Chronic Health Evaluation)-II scores, serum NSE and S100 protein levels, and mortality did not differ significantly between the groups ($p > 0.05$; Table 1). However, a significant difference in BIS values was found between the groups ($p < 0.05$; Table 1).

We further investigated the correlation between BIS values and NSE and S100 protein levels in these patients. BIS values correlated negatively with NSE protein levels ($r = -0.318$, $p = 0.004$), and S100 protein levels ($r = -0.576$, $p < 0.001$; Fig. 1). ROC curve analysis was used to assess the discriminating performance of BIS values, NSE, and S100 protein levels to predict the death of patients (Fig. 2). The area under the curve (AUC) and the optimal cutoff value were calculated. The AUCs for BIS value, NSE level, and S100 protein level were 0.841 ($p < 0.001$, 95 % CI = 0.751–0.931), 0.713 ($p = 0.002$, 95 % CI = 0.582–0.844), and 0.790 ($p < 0.001$, 95 % CI = 0.680–0.899), respectively. For the BIS value, the optimal cutoff value to predict death within 2 weeks was 32.5 (sensitivity = 60.4 %, specificity = 100 %, positive predictive value = 100 %, negative predictive value = 67.2 %, and accuracy = 77.8 %).

Table 1 Bispectral index (BIS) values, neuron-specific enolase (NSE) levels, and S100 protein levels by different causes of brain injury

Cause	*n*	Age (years)	GCS	APACHE II	BIS value	NSE (mg/dl)	S100 protein (ng/l)	Mortality
Cerebral hemorrhage	15	64 (27)	3 (1)	26 (46)	11 (41)	54.37 (122.73)	3.79 (8.45)	10/15
Brainstem hemorrhage	9	42 (24.5)	3 (1.5)	27 (16)	46 (54.5)	36.33 (109.83)	2.33 (7.94)	7/9
Subarachnoid hemorrhage	8	65 (22.3)	3 (2.25)	28 (62.75)	40.5 (56.5)	41.11 (52.2)	2.30 (4.52)	4/8
Cerebral infarction	13	65 (28)	4 (2)	23.5 (19)	49 (56.5)	64.11 (134.81)	2.79 (6.42)	7/13
Head injury	9	60 (32.5)	3 (1.5)	24 (7.5)	8 (42.5)	108.05 (238.65)	2.55 (3.92)	6/9
Hypoxic ischemic encephalopathy (HIE) after cardiac arrest	27	70 (17)	3 (2)	31 (10)	63 (16)*	79.26 (300.5)	1.17 (4.47)	12/27
Cerebral anoxia after shock	9	68 (54)	3 (2.5)	25 (14.5)	47 (23)*	33.56 (31.09)	0.57 (0.87)	2/9
p		0.193	0.915	0.529	<0.001	0.277	0.233	0.122

Data are presented as medians (quartile range)*GCS* Glasgow Coma Scale

* $p < 0.05$ vs. cerebral hemorrhage

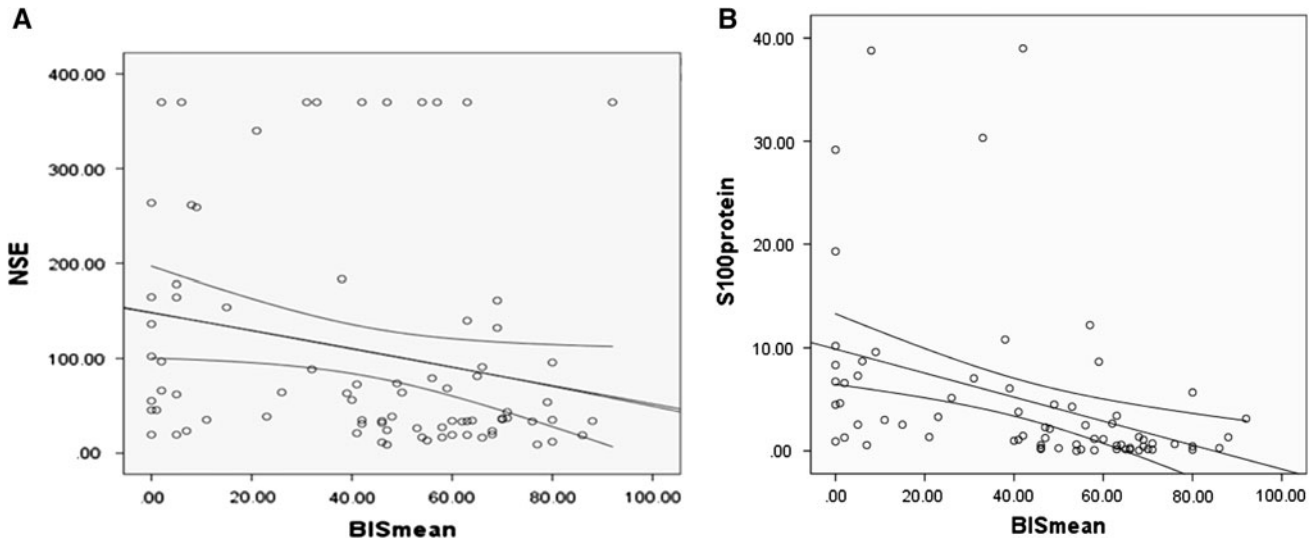

Fig. 1 Correlation between mean bispectral index (*BIS*) values and serum neuron-specific enolase (*NSE*) (**a**) and *S100* protein (**b**) levels. BIS values correlated negatively with NSE protein levels ($r = -0.318$, $p = 0.004$) and S100 protein levels ($r = -0.576$, $p < 0.001$). Note *regression line* and 95 % CI

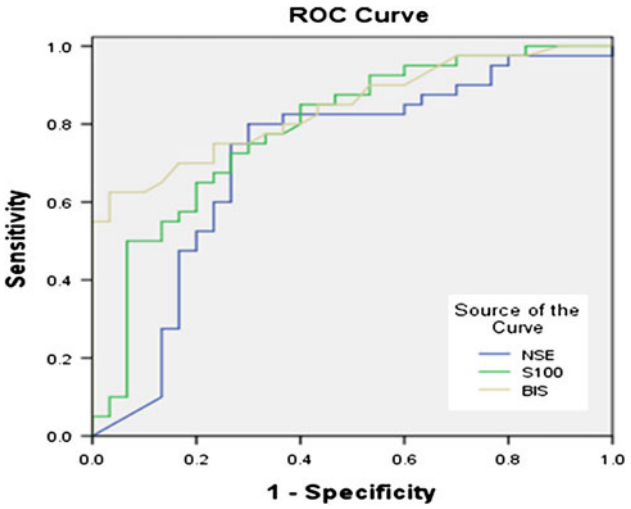

Fig. 2 *ROC curves* for BIS, NSE, and S100 protein for predicting death within 2 weeks in patients with brain injuries

According to the optimal cutoff BIS value, patients were divided into two groups: patients with a BIS value ≤32.5 and patients with a BIS value >32.5. Table 2 shows the age, NSE and S100 protein levels, and the mortality of patients in the two groups. The serum NSE and S100 protein levels and the mortality rate were significantly lower in patients with a BIS value >32.5 compared with those in patients with a BIS value ≤32.5 ($p < 0.05$; Fig. 3, Table 2). Additionally, the average age of patients with a BIS value >32.5 was significantly older than that of patients with a BIS value ≤32.5 ($p = 0.024$). We then used two-way ANOVA to test the effect of the patient's age on prediction of death within 2 weeks by BIS. The patient's age did not have a significant effect on the prediction of death within 2 weeks by BIS [two-way ANOVA, F (1, 86) = 0.031, $p = 0.860$]. In addition, it has been reported that older age is associated with worse outcome in patients with brain injuries [19–22]. However, patients with a BIS value >32.5 were older and associated with a lower mortality rate, suggesting that age was not a contributing factor affecting the ability of BIS to predict deaths within 2 weeks in coma patients.

We then tested whether the optimal cutoff BIS value of 32.5 was valid for prediction of death within 2 weeks in patients with each cause of brain injury (Table 3). For patients with brain injuries caused by cerebral hemorrhage, cerebral infarction, and head injury, the mortality rate was significantly lower in patients with a BIS value >32.5 compared with those in patients with a BIS value ≤32.5 ($p < 0.05$; Table 3). For patients with other causes of brain injuries, no significant difference in the mortality rate was found between patients with a BIS value >32.5 compared with those in patients with a BIS value ≤32.5, though patients with a BIS value >32.5 had a tendency to exhibit a low mortality rate.

Discussion

The assessment of outcomes in coma patients with severe brain injuries represents a significant challenge. The Glasgow Coma Scale (GCS) is commonly used to evaluate the degree of coma. In this study, we found that GCS scores did not differ significantly among patients with different causes of brain injury, suggesting similar degrees of coma. We further investigated the BIS values and serum levels of NSE and S100 protein in 90 coma patients. We found that BIS values correlated negatively with serum NSE and S100 protein levels, and the mortality rate within 2 weeks was significantly lower in patients with BIS values above the cutoff value of 32.5 versus patients with a BIS value ≤32.5. Our data suggest that a BIS value >32.5 is associated with favorable outcomes in coma patients with various causes of brain injury.

NSE and S100 protein are considered promising markers of brain damage. Several studies have shown that serum NSE and S100 protein levels are prognostic predictors in patients with brain injuries [3, 4, 23, 24], although the specificity and sensitivity of serum NSE and S100 protein levels have been questioned by some researchers [8, 9, 25]. Pelinka et al. reported that serum NSE increased in non-nervous tissue damage [25], suggesting that NSE was not a specific marker for brain injury. In this study, we only included coma patients with severe brain injuries and excluded coma patients with other diseases, suggesting that serum NSE levels did reflect brain injury in our study. Additionally, Kleine et al. [26] reported that an increase in the serum S100B protein level together with a normal NSE level indicated nonnervous tissue damage. Our findings that both serum NSE and S100 protein levels increased further suggest that brain injury was the major causes of coma in this study. We also found that BIS values correlated negatively with serum NSE and S100 protein levels,

Table 2 Different BIS values by NSE and S100 protein [M(Q)]

Group	*n*	Age (years)	NSE (mg/dl)	S100 protein (ng/l)	Mortality
BIS value ≤32.5	29	56 (14.75)	99.5 (214.14)	5.87 (6.37)	100 % (29)
BIS value >32.5	61	69 (27.5)	35.46 (65.3)	1.04 (2.74)	32.8 % (20)
p		0.024	0.035	0.026	<0.001

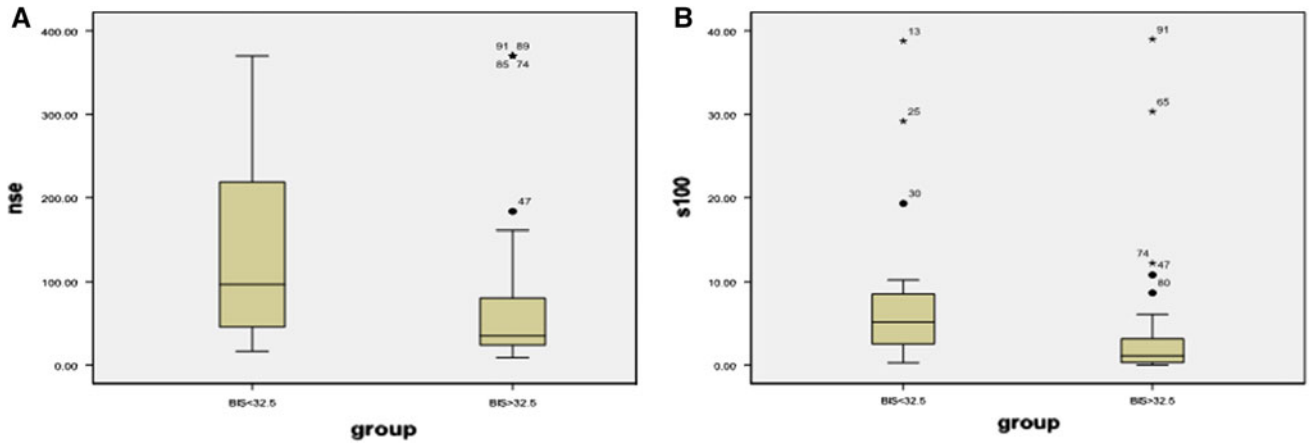

Fig. 3 NSE (**a**) and S100 (**b**) levels in coma patients with a BIS value >32.5 and coma patients with a BIS value ≤32.5

Table 3 Application of BIS value of 32.5 in patients with each cause of brain injury

Cause	*n*	BIS ≤ 32.5, alive/dead	BIS > 32.5, alive/dead	*p*
Cerebral hemorrhage	15	0/8	5/2	0.001*
Brainstem hemorrhage	9	0/3	2/4	0.107
Subarachnoid hemorrhage	8	1/3	3/1	0.148
Cerebral infarction	13	0/5	7/1	0.001*
Head injury	9	0/6	2/1	0.017*
HIE after cardiac arrest	27	1/4	14/8	0.071
Cerebral anoxia after shock	9	0/0	7/2	NA

Chi-square test, * $p < 0.05$

suggesting that BIS values can be used as a parameter for evaluating brain injury.

We also compared the effectiveness of BIS values and serum NSE and S100 protein levels in predicting death within 2 weeks in these coma patients, using ROC curve analyses. We found that the AUC for the BIS value (0.841) was higher than that for NSE (0.713) or S100 (0.790), suggesting that BIS values showed more accurate prediction of death with 2 weeks than serum NSE or S100 levels. Additionally, we used the Youden index (defined as sensitivity + specificity − 1) to obtain the optimal BIS value, the threshold value for which sensitivity + specificity − 1 was maximized. The optimal cutoff BIS value (32.5) with high specificity (100 %) and a positive predictive value (100 %) suggested that the coma patients who survived beyond 2 weeks had high BIS values. The low sensitivity (60.4 %) may have been associated with the complex causes of deaths in these coma patients with severe brain injuries. Although we excluded deaths from extracerebral lesions, we cannot exclude the possibility of death caused by rapid exacerbation of preexisting extracerebral diseases in these critically ill patients.

BIS has been used in the clinic as a measure of hypnotic effect, depth of anesthesia, and depth of sedation [10, 11, 27–30]. Higher BIS values have been reported to predict a better outcome [12, 13, 15, 16]. Stammet et al. [18] reported that no correlation was found between good outcomes and BIS values higher than zero. That study found a wide range of BIS values, but no cutoff BIS value was determined, which may have affected the conclusions. In this study, we identified the optimal cutoff value of 32.5 for predicting death within 2 weeks. The serum NSE and S100 protein levels were significantly lower in patients with a BIS value >32.5 compared with those in patients with a BIS value ≤32.5, suggesting that the optimal cutoff value of 32.5 may reflect the level of brain injury and is a good predictor of deaths within 2 weeks in coma patients. In addition, we found that the optimal cutoff value of 32.5 could predict death within 2 weeks in patients with brain injuries caused by cerebral hemorrhage, cerebral infarction, and head injury. Although no significant difference in the mortality rate was found between patients with a BIS value >32.5 and patients with a BIS value ≤32.5, patients with a BIS value >32.5 tended to exhibit a low mortality rate. A large sample size of patients may be required to further test the effect of the optimal cutoff value of 32.5 in prediction of deaths within 2 weeks in patients with each cause of brain injury.

Zandbergen et al. [24] reported that the cutoff value for prediction of poor prognosis in anoxic-ischemic coma was 33 ng/ml for serum NSE and 0.7 ng/ml for serum S100 protein. Using these cutoff values of 33 ng/l for serum NSE and 0.7 ng/ml for serum S100 in combination with the BIS cutoff value of 32.5, the accuracy of prognosis can increase to 94.5 %, from 78 % as calculated with the BIS cutoff value alone. Thus, using the electrophysiological measures

in combination with biochemical biomarkers will improve prognostic accuracy.

Our study included coma patients with various causes of severe brain injury. Patient age, serum NSE and S100 protein levels, and mortality did not differ significantly among the patients with different causes of brain injury, suggesting that the severity of brain injury did not differ among the patients with different causes. The BIS values did differ significantly among patients with different causes, mainly because patients with cerebral hemorrhage and head injuries had significantly lower BIS values, suggesting that cerebral hemorrhage and damage block the ascending reticular activating system, resulting in coma. Thus, BIS may reflect the severity of brain injury and the state of consciousness more accurately than serum NSE or S100 protein levels.

In this study, BIS monitoring was performed at an early stage of coma (within 12 h after brain injury). However, we used peak serum NSE and S100 protein levels that were measured later than the BIS measurement. It has been reported that peak serum NSE and S100 protein levels showed the highest positive predictive values for brain injury [24, 31]. In this study, we sought to find any correlation between BIS values and brain injury in predicting patient deaths. Thus, we selected peak serum NSE and S100 protein levels, which may best reflect and predict the status of brain injury. The time lag between BIS value measured and peak serum NSE and S100 protein levels measured does not affect our conclusion that BIS value is a good prognostic predictor of death within 2 weeks in coma patients with severe brain injuries. Instead, early BIS monitoring showed an advantage over serum NSE and S100 protein levels in the early prediction of deaths in coma patients.

In conclusion, the present study demonstrates that BIS values correlate with serum NSE and S100 levels and are a good prognostic predictor of death within 2 weeks in coma patients with severe brain injuries. A cutoff BIS value of 32.5 was identified. These results indicate that BIS is an objective and noninvasive monitoring method for helping clinicians to predict death in coma patients.

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