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Prediction of neurological outcome using bispectral index in patients with severe acute brain injury

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Aim: To predict consciousness recovery and outcome of patients with severe acute brain injury using the bispectral index (BIS).

Materials and methods: A prospective study of 189 brain-injured patients was made when they were without sedatives for at least 24 h. BIS, 95% spectral edge frequency (SEF), burst suppression ratio (SR), total power (TP), spontaneous electromyographic activity (EMG), and signal quality index (SQI) were recorded continuously for 30 min. Neurologic conditions were measured with the Glasgow Coma Score (GCSBIS) when recording BIS. Patients were followed for 30 days after injury to assess consciousness recovery and outcome.

Results: There were statistically significant differences in BIS measurements between patients that recovered consciousness or survived and those who did not. The best correlation coefficients for patients' outcome were 0.738 for GCSBIS, 0.639 for SR, and 0.591 for BIS. As to the patients' consciousness recovery, the best coefficients were 0.656 for GCSBIS, 0.526 for BIS, and 0.511 for SR. According to the area under the receiver operating characteristic curve, the best values to predict consciousness recovery and survival were GCSBIS and BIS, and for unconsciousness and death, the best parameters were SR, APACHE II score, and SEF.

Conclusion: BIS measurement is useful to predict consciousness recovery and outcome in severe acute brain injury.

Key words: Bispectral index, brain injury, outcome, recovery

1. Introduction

If the outcomes of acutely brain-injured patients can be predicted, then the clinical care delivered to them can be better addressed. Unfortunately, it is difficult to know their neurological outcomes in advance. Unfortunately we do not have a reliable prognostic indicator and predictions are usually dependent on clinical signs such as the Glasgow Coma Score (GCS). Because motor responses may be minimal or undetectable, the objective assessment of residual cognitive function in patients with severe acute brain injury is extremely difficult. Many methods, including auditory evoked potentials, electroencephalogram (EEG), and somatosensory-evoked potentials, have been used to predict neurological outcome in patients with brain injuries. Traditional electroencephalography has been shown to efficiently predict outcome after anoxic or traumatic brain injury (1–4). However, it is currently not possible to disentangle altered neurological states solely based on EEG (5) and the analyses of EEGs require expertise and much time. Moreover, unprocessed electroencephalography often reports global brain damage, and evoked potential studies are also of little help in specific settings (1).

The bispectral index (BIS), a processed electroencephalographic monitoring device, is widely used in the operating room to guide anesthesia and to improve the recovery process (6–10). The BIS is also used for sedation assessment in critically ill patients (11–16). Although the BIS has not been developed for use in patients with neurologic disorders, some published studies have focused on brain injured patients (17–24). BIS monitoring may contribute to the identification of patients with severe brain injury who have no realistic chance of a good recovery. Conversely, using existing predictors, some patients may be judged incorrectly and thus may be treated erroneously. The predictive ability of consciousness recovery and outcome in comatose patients due to severe acute cerebral damage has not been validated thoroughly; we therefore planned to validate it in a greater population.

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2. Materials and methods

This prospective trial was carried out in compliance with the Helsinki Declaration and was approved by the local Institutional Review Board. It was performed consecutively on 189 acutely brain-injured adult patients. Informed consents were obtained from the patients' surrogate decision makers. These patients were treated in a 21-bed comprehensive Intensive Care Unit (ICU) in a 2200-bed university hospital. In this ICU, approximately 500 patients with brain injuries are admitted per year. All patients included in the study were unconscious and unable to respond to verbal commands. They had not received anesthetics or sedatives for at least 24 h before the study day. On admission to the ICU, a number of data were recorded: sex, age, computed tomography scan, type of brain lesion, Acute Physiology and Chronic Health Evaluation II (APACHE II) severity score, cause of death, and days from injury to the day of study. Bispectral index recording was performed by means of a BIS XP monitor (Aspect Medical Systems, Inc., Newton, MA, USA) with a 4-electrode sensor (BIS sensor; Aspect Medical Systems, Inc.). BIS, 95% spectral edge frequency (SEF), total power (TP), burst suppression ratio (SR), spontaneous electromyographic activity (EMG) in the frontal area, and signal quality index (SQI) were recorded continuously directly from the output of the BIS XP monitor for 30 min. The average values of these parameters were recorded when the SQI was best. The patients' neurologic status was assessed by the GCS at the moment of BIS measurement (GCS_{BIS}). Patients were then followed for 30 days after injury or until they died. Consciousness recovery was evaluated by measuring the ability of the patient to respond to verbal commands, independently of the degree of patient's disability. Glasgow Outcome Score (GOS) was used to define the neurologic status at the end of the follow-up period.

2.1. Statistical analysis

All normally distributed values are expressed as mean ± standard deviation and nonnormally distributed values are expressed as median and interquartile range. Patients were divided into 2 groups according to their consciousness recovery. The values of BIS, TP, SEF, SR, EMG, and SQI, as well as the clinical indicators measured on the study day (APACHE II, GCS_{BIS}), were compared between groups by means of the Mann–Whitney U test. The patients who survived and those who died were also analyzed as independent groups. Statistical significance was considered when $P < 0.05$.

Relationship assessments between variables were performed using the Spearman correlation coefficient. The area under the receiver operating characteristic curve (AUC) with 95% confidence intervals (95% CI) was used as an estimate of predictive ability. Optimal cutoff point values to predict outcome for the parameters were determined using the maximum Youden index (J = sensitivity + specificity – 1) (25). All analyses were done using SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

3. Results

There were 130 men and 59 women consecutively included in this study. Table 1 summarizes the main demographic characteristics of the patients. Brain injury was due to brain trauma in 79 cases, cerebral hemorrhage in 58

Table 1. Demographic characteristics, BIS derivative parameter results, and neurologic assessment (n = 189).

Male sex	130 (68.8)
Age, years	51 (40, 63.5)
Cause of brain injury	
Traumatic brain injury	79 (41.8)
Cerebral hemorrhage	58 (30.6)
Cerebral infarction	10 (5.3)
Subarachnoid hemorrhage	20 (10.6)
Cardiopulmonary resuscitation	22 (11.6)
APACHE II	17 (14, 22)
SQI	100 (95, 100)
EMG	32 (27, 39)
SEF	12.8 (8.0, 20.5)
TP	55 (43, 60)
BIS	47 (17, 62)
SR	0 (0, 64)
Outcome at the 30th day	
Died	92 (48.7)
Survived	97 (51.3)
Recovery at the 30th day	
Conscious	63 (33.3)
Unconscious or died	126 (66, 7)
Days from injury to BIS measurement	2 (1, 5)
GCS_{BIS}	5 (3,6)
Days from BIS measurement to death	2 (1, 4.25)
GOS - end follow-up	5 (3, 5)
Days followed	2 (2, 32)

Data are median (interquartile range) or number (%).

cases, subarachnoidal hemorrhage in 20 cases, cerebral infarction in 10 cases, and cardiopulmonary resuscitation in 22 cases. According to the patients' conditions, routine treatment was given and the necessary surgeries were performed for evacuating cerebral hematoma, clipping of aneurysms, embolization of intracerebral aneurysms, or placement of an external ventricular drainage. Table 1 also shows the values of BIS, SR, TP, 95% SEF, SQI, and EMG, as well as the neurologic examination at the time of BIS measurement (GCS_{BIS}). Days from injury to BIS recording, consciousness recovery and outcome at the 30th day after injury, GOS at the end of the follow-up period, and days of follow-up are also shown in the same table. The severity of the neurologic situation in this study population is supported by the fact that 92 patients had died, most of them during the first few days after brain injury, and 126 patients were unconscious or had died by the 30th day. The cause of death was brain death, or death was directly attributable to severe brain damage, in all patients. The degree of neurologic impairment of patients at BIS measurement (GCS_{BIS}) and at the end of follow-up (GOS) can be observed in Table 1.

No differences were found in demographic characteristics between the patients who had good outcomes (recovered consciousness or survived) and those who had poor outcomes (reached a vegetative state or died) (Table 2); however, with respect to BIS, SR, TP, EMG, and SQI values, there were statistically significant differences between groups. There were also significant differences between groups with respect to $GCS_{BIS,}$ APACHE II, and GOS at the 30th day. SQI and SR were significantly higher and BIS, EMG, and GCS_{BIS} were lower in the poor-outcome group ($P < 0.05$), the lower EMG probably being related to lower muscle activity in these patients.

Table 3 shows the correlations between BIS derivative parameters, neurologic examination, and APACHE II and the patients' prognosis by Spearman's correlation test. As to the patients' outcome at the 30th day (dead or surviving), the higher correlation coefficients were for GCS_{BIS}, SR, BIS, and APACHE II. As to the patients' recovery at the 30th day (conscious or unconscious), the higher correlation coefficients were for GCS_{BIS}, BIS, SR, and APACHE II. For the GOS at the end of the follow-up period, the higher correlation coefficients were for GCS_{BIS}, SR, BIS, and APACHE II.

According to the AUC, the best values to predict consciousness at the 30th day were 0.886 for GCS_{BIS}, 0.882 for BIS, 0.746 for EMG, and 0.737 for TP (Table 4; Figure 1). The cutoff points to predict consciousness were 4.5 for GCS_{BIS}, 34.5 for BIS, 33.5 for EMG, and 49 for TP (Table 4; Figure 1). From Table 4, we can see that the best parameters to predict unconsciousness were APACHE II, SR, and SQI with the AUC, values being 0.800, 0.780, and 0.592, respectively. The cutoff points were 17.5 for

Table 2. Comparisons between both groups studied.

	Consciousness recovery		P	Outcome		P
	Conscious	Unconscious		Survived	Died	
Sex (M/F)	39/24	91/35	0.150	67/30	91/35	0.930
Age	53 (40, 67)	50 (40, 63)	0.446	53 (44, 64)	48.5 (40, 63)	0.254
Days from injury to BIS measurement	2 (1, 5)	2 (1, 5.3)	0.678	2 (1, 7)	2 (1, 7)	0.245
SQI	97 (92, 100)	100 (97.8, 100)	0.025	97 (92, 100)	100 (97.8, 100)	0.000
EMG	38 (33, 43)	29.5 (26, 35)	0.000	36 (30, 42)	29.5 (26, 35)	0.000
SEF	10.9 (8, 17.3)	13.5 (8.5, 21.5)	0.057	10 (7.8, 16)	13.5 (8.5, 21.5)	0.000
TP	59 (55, 62)	50 (40.8, 58)	0.000	57 (54, 61.5)	50 (40.8, 58)	0.000
BIS	62 (49, 74)	34.5 (2.8, 52)	0.000	60 (45.5, 68.5)	34.5 (2.8, 52)	0.000
SR	0 (0, 0)	6.5 (0, 94)	0.000	0 (0, 0)	6.5 (0, 94)	0.000
APACHE II	14 (11, 17)	20 (16, 25)	0.000	15 (12, 18)	20 (16, 25)	0.000
GCS_{BIS}	7 (6, 9)	3 (3, 5)	0.000	6 (5, 8)	3 (3, 5)	0.000
GOS	2 (1, 3)	5 (4.8, 5)	0.000	3 (1, 4)	5 (4.8, 5)	0.000
Days of follow-up	31 (30, 63)	3 (1, 17)	0.000	32 (24.5, 61.5)	3 (1, 17)	0.000

Table 3. The correlation between BIS derivative parameters and prognosis (Spearman's correlation).

	Outcome	Recovery	GOS
SQI	0.285**	0.164*	0.288**
EMG	0.406**	0.403**	0.434**
SEF	0.298**	0.139	0.223**
TP	0.443**	0.388**	0.435**
BIS	0.591**	0.526**	0.618**
SR	0.639**	0.511**	0.620**
APACHE II	0.500**	0.491**	0.574**
GCS_{BIS}	0.738**	0.656**	0.787**

*: P < 0.05, **: P < 0.01.

Table 4. Receiver-operator characteristic (ROC) curve of BIS derivative parameters to predict consciousness recovery.

	Consciousness prediction						Unconsciousness prediction					
	AUC	P	95% CI	Cutoff point	Sensitivity	Specificity	AUC	P	95% CI	Cutoff point	Sensitivity	Specificity
GCS_{BIS}	0.886	0.000	0.837–0.935	4.5	0.952	0.713	0.114	0.000	0.065–0.163			
BIS	0.822	0.000	0.764–0.880	34.5	1.0	0.5	0.178	0.000	0.120–0.236			
EMG	0.746	0.000	0.675–0.818	33.5	0.746	0.706	0.254	0.000	0.182–0.325			
TP	0.737	0.000	0.665–0.809	49	0.921	0.484	0.263	0.000	0.191–0.335			
SEF	0.415	0.057	0.332–0.498				0.585	0.057	0.502–0.668			
SQI	0.408	0.039	0.320–0.495				0.592	0.039	0.505–0.680	97.5	0.619	0.571
SR	0.220	0.000	0.157–0.283				0.780	0.000	0.717–0.843	0.5	0.595	0.937
APACHE II	0.200	0.000	0.135–0.264				0.800	0.000	0.736–0.865	17.5	0.651	0.841

APACHE II, 0.5 for SR, and 97.5 for SQI (Table 4; Figure 2). Table 5 shows the parameters used to predict patients' outcome (dead or surviving at the 30th day), and according to the AUC, the best parameters to predict death were SR, APACHE II, SEF, and SQI, which were similar to those predicting unconsciousness. The better parameters to predict survival, similar to those predicting consciousness, were GCS_{BIS}, BIS, EMG, and TP (Figure 3 and 4).

4. Discussion

Since its introduction in clinical practice, the BIS has been widely used in the operating room and ICU settings. However, the ability of the BIS to provide clinical insight in the absence of hypnotic drugs has not been extensively studied. Although the BIS was not designed to be applied in brain-injured ICU patients, its availability in the ICU has led to many studies focusing on this population (21–24), but most of these were conducted using a small group of participants.

In our study, 189 comatose patients were studied. None of them received any drugs that may affect conscious judgment for at least 24 h before BIS recording. Our patients were followed until they died or for at least for 30 days. We also included different etiologies of severe brain injury.

In our study, we found that BIS derivative parameters were significantly different between patients who recovered consciousness or survived and those with poor neurologic outcome (unconsciousness or death). There were statistically significant differences (P < 0.05) between

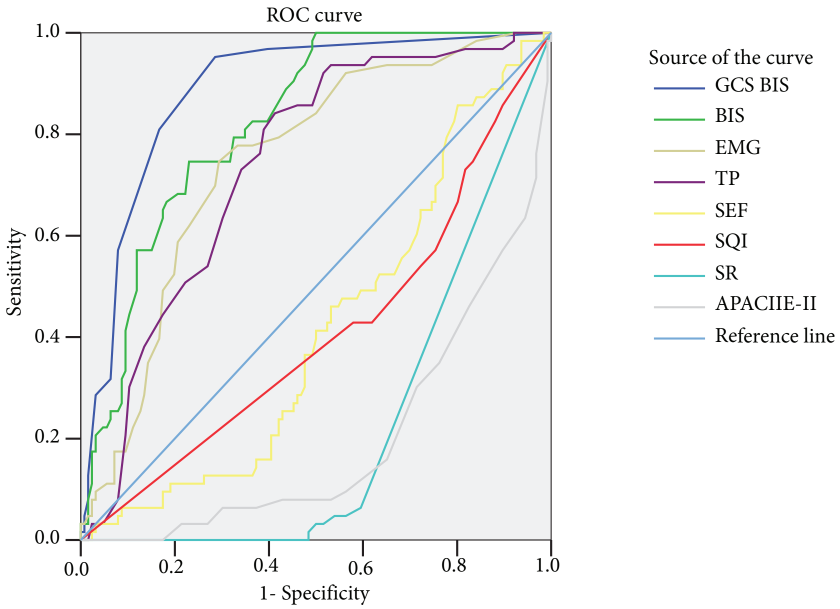

Figure 1. ROC curve for BIS derivative parameter to predict consciousness.

Table 5. Receiver-operator characteristic (ROC) curve of BIS derivative parameters to predict outcome.

	Survival prediction						Death prediction					
	AUC	P	95% CI	Cutoff point	Sensitivity	Specificity	AUC	P	95% CI	Cutoff point	Sensitivity	Specificity
GCS_{BIS}	0.909	0.000	0.865–0.954	4.5	0.856	0.859	0.091	0.000	0.046–0.135			
BIS	0.841	0.000	0.783–0.899	34.5	0.948	0.630	0.159	0.000	0.101–0.217			
TP	0.755	0.000	0.683–0.828	52.5	0.804	0.717	0.245	0.000	0.172–0.317			
EMG	0.734	0.000	0.662–0.807	28.5	0.856	0.500	0.266	0.000	0.193–0.338			
SQI	0.349	0.000	0.270–0.427				0.651	0.000	0.573–0.730	97.5	0.717	0.598
SEF	0.328	0.000	0.249–0.406				0.672	0.000	0.594–0.751	10.95	0.728	0.557
APACHE II	0.212	0.000	0.148–0.276				0.788	0.000	0.724–0.852	18.5	0.641	0.814
SR	0.170	0.000	0.108–0.232				0.830	0.000	0.768–0.892	9.5	0.630	0.969

the groups in BIS, SR, EMG, SQI, and TP when patients who recovered consciousness or survived were compared with patients who did not. The BIS, EMG, and TP in the good neurologic outcome group were significantly higher than those in the poor neurologic outcome group, while SR and SQI were lower. We found a significant correlation between BIS measurement and outcome or recovery. Thus, BIS derivative parameters were useful in predicting neurologic outcome, but no better than the traditional clinical measures usually employed in this population, such as the GCS. Myles et al. reported that the BIS provides useful information that may identify patients with a good chance of recovery after ischemic hypoxic brain injury requiring emergency surgery when compared with clinical judgment and routine laboratory tests (22). Many studies have evaluated the accuracy of BIS monitoring for the diagnosis of brain death in severely comatose patients. These studies indicated that the BIS shows a perfect correlation with other diagnostic methods such as transcranial Doppler imaging and EEG in the diagnoses of brain death, and that BIS is a useful tool to detect the beginning of brain herniation but cannot be used on its own for the confirmation of brain death (26–29). In our study, based on Spearman's correlation test,

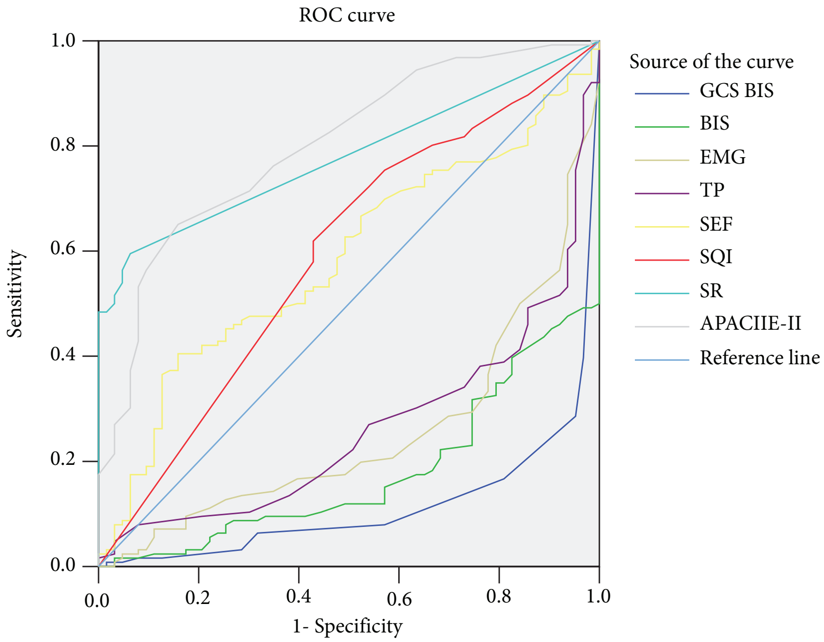

Figure 2. ROC curve for BIS derivative parameters to predict unconsciousness.

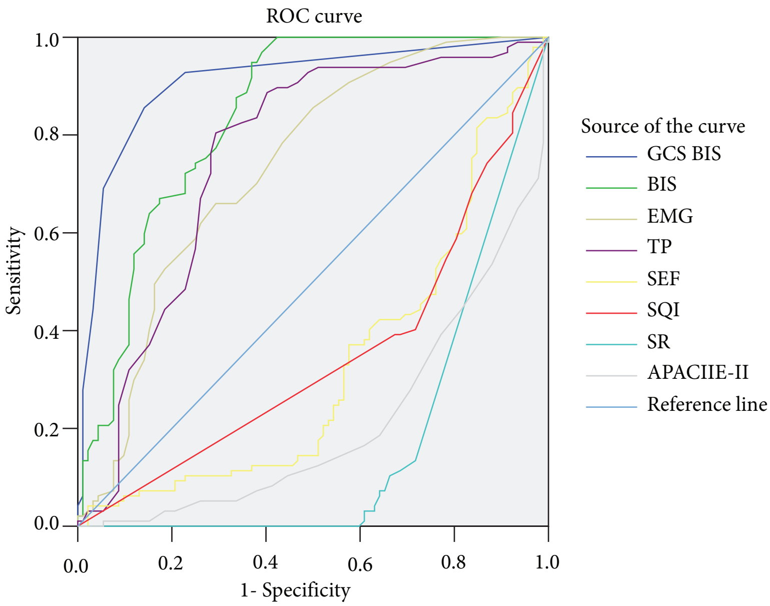

Figure 3. ROC curve for BIS derivative parameters to predict survival.

BIS was closely correlated with patients' consciousness, survival, and GOS at the 30th day, and BIS measurement was a useful tool to predict conscious (AUC = 0.882, cutoff point = 34.5) and survival (AUC = 0.841, cutoff point = 34.5). Theilen et al. observed that SR could be correlated with 6-month outcomes after severe traumatic brain injury, while Fàbregas et al. (30) thought, based on a small sample study, that SR could not help to discriminate which patients would recover consciousness. However, based on our results, we found that SR was closely correlated with patients' outcomes and was a good parameter to predict death (AUC = 0.830, cutoff point = 9.5) and unconsciousness (AUC = 0.780, cutoff point = 0.5).

EMG testing and its interference in BIS recording have been an increasing concern. It was shown showed that the BIS may be lower in patients with paralysis for deep

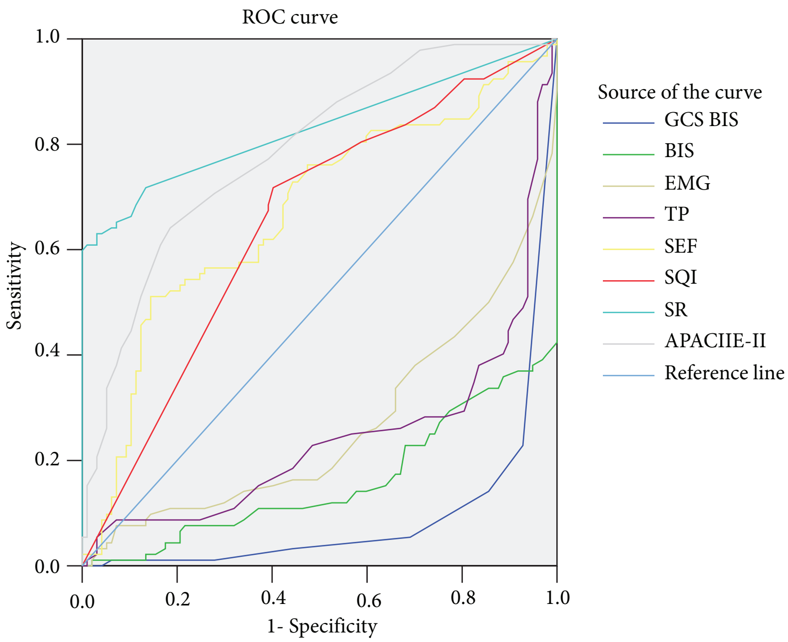

Figure 4. ROC curve for BIS derivative parameters to predict death.

sedation and that neuromuscular blockade can induce a significant decrease in BIS values. It is logical that the patients likely to recover consciousness will have more muscular activity than those who do not. Fàbregas et al. (30) found that EMG had a strong prediction probability of consciousness recovery. In our study, no patients were under hypothermic blanket therapy or any other special electrical device known to potentially increase BIS readings, and no neuromuscular blocking drugs were used. We used the newer version of the BIS, BIS XP, which was specially designed to discriminate and reject artifacts such as patient movement, and we still found that EMG was closely correlated with patients' consciousness recovery and survival based on Spearman's correlation test and the AUC of the ROC. Thus, EMG may be a potentially useful tool in predicting patients' outcome in acute brain injury, but this may need more trials to be validated.

We are aware some limitations of our study. We recorded the BIS only at the initial period after brain injury for a short time of 30 min when the patients' neurological states were not stable, such that the results of the BIS recordings were also not stable. This may dramatically affect the predictive ability of BIS and the correlation of BIS with patients' outcome. Further research using repetitive or continuous BIS monitoring may get more incentivizing results in patients with acute brain injury.

This study indicated that BIS was related to consciousness recovery and outcome, and it can be used to predict consciousness recovery and outcome in severe, acute brain-injured patients, measured when patients are without sedation. However, the interpretation of BIS in an ICU situation may be complicated, and so these results may encourage the conducting of more in-depth, detailed trials to validate them.

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