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Brain symmetry index predicts 3-month mortality in patients with acute large hemispheric infarction

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Abstract

Quantitative electroencephalography data are helpful to predict outcomes of cerebral infarction patients. The study was performed to evaluate the value of brain symmetry index by quantitative electroencephalography in predicting 3-month mortality of large hemispheric infarction. We studied a prospective, consecutive series of patients with large supratentorial cerebral infarction confirmed within 3 days from the onset in 2 intensive care units from August 2017 to February 2020. The electroencephalography was recorded once admission. The brain symmetry index (BSI) which is divided into BSIfast and BSIslow were calculated for each electrodes pair. The outcome was mortality at 3 months after the onset. A total of 38 patients were included. The subjects were divided into the mortality group (15 patients) and survival group (23 patients). Of the BSIfast and BSIslow at each electrodes pair, higher BSIfastC3–C4, higher BSIslowC3–C4, and higher BSIslowO1–O2 were noticed in the mortality group than that in the survival group at 3 months ($P = .001$; $P = .010$; $P = .009$). Multivariable analysis indicated that BSIfastC3–C4 was an independent predictor of 3-month mortality (odds ratio = 1.059, 95%CI 1.003, 1.119, $P = .039$). BSIfastC3–C4 could significant predict 3-month mortality (area under curve = 0.805, $P = .005$). And when we combined BSIfastC3–C4, Glasgow Coma Scale and infarct volume together to predict the 3-month mortality, the predicted value increased (area under curve = 0.840, $P = .002$). BSIfastC3–C4 could independently predict the 3-month mortality of large hemispheric infarction. The combination marker which includes Glasgow Coma Scale, infarct volume, and BSIfastC3–C4 has a better diagnostic value. Further clinical trials with a large sample size are still needed.

Abbreviations: AUC = area under curve, BSI = brain symmetry index, EEG = electroencephalography, LHI = large hemispheric infarction, QEEG = quantitative electroencephalography.

Keywords: brain symmetry index, infarct volume, large hemispheric infarction, prognosis, quantitative electroencephalogram

1. Introduction

Large hemispheric infarction (LHI) is a life-threatening ischemic stroke with a high mortality rate of approximately 60.9 to 78% in conservatively treated patients.[1] Patients might benefit from decraniectomy if the poor prognosis could be identified early.[2,3]

Quantitative electroencephalography (QEEG), originated from raw electroencephalography (EEG) data, provides a quantitative analysis of the data both in the frequency and the time domain. It transforms graphic EEG elements into calculated parameters, simplifying the interpretation and allowing the analysis to be more objective.[4] It has the advantage of being convenient for long-range monitoring and convenient use for non-EEG professionals. Clinical studies reveal that QEEG parameters in stroke patients changed before clinical changes.[5–7] At present, articles focusing on the outcome prediction of LHI at an early time by QEEG remain scarce. Two case-report studies reported an increase of delta power in the contralateral hemisphere suggested a poor prognosis.[5] Mengdi Jiang et al[8] found that the contralateral theta power could predict short-term (at discharge) nonsurvival outcomes in LHI. Most of these results suggest that the QEEG parameters representing the contralateral cerebral hemisphere may predict an early outcome, yet no suitable predictive index for long-term prognosis has been found. So the asymmetry of QEEG parameters between the ipsilateral and contralateral hemispheres may be valuable for the prognosis of LHI. Because of this, the brain symmetry index (BSI), which represents the asymmetry between the hemispheres by calculating

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

This study was approved by the Ethics Committees of the Beijing Tiantan Hospital and the Second Hospital of Hebei Medical University.

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the differences of power at each electrodes pair,[7] may be the promising predictor. Higher BSI is often associated with worse outcomes in strokes.[9,10]

The purpose of this study was to evaluate BSI at each electrodes pair and in different frequency range in predicting LHI mortality at 3-month to early provide an opportunity for intervention strategies.

2. Materials and Methods

2.1. Study subjects

Patients with LHI confirmed by head computed tomography (CT) or magnetic resonance imaging from August 2017 to February 2020 in the Neurointensive Care Unit of Beijing Tiantan Hospital and the Second Hospital of Hebei Medical University were enrolled. Inclusion criteria were patients older than 18 years; patients who were admitted to the neurological intensive care unit within 3 days after the stroke onset; infarction involved at least 2/3 of the middle cerebral artery territory based on CT or magnetic resonance imaging. Exclusion criteria were: patients with multiple infarctions of the cerebellum, brain stem, or bilateral cerebral hemispheres; patients who received antiepileptic drugs which may affect brain electrical activity within 24 hours before EEG monitoring; patient's pre-onset modified Rankin Scale ≥ 2 points; patients who had significant diseases that seriously affect the prognosis, such as severe heart failure at the time of onset. Written informed consent was obtained from all the subjects and/or their legal representatives. This study was approved by the Ethics Committees of the Beijing Tiantan Hospital and the Second Hospital of Hebei Medical University.

2.2. Experimental methods

2.2..1. EEG monitoring. The patients were monitored by using a digital video EEG monitor (Nicolet Monitor, Natus®) within 3 days after onset, for at least 2 hours each time, and at least once for each case. The monitoring was performed in the intensive care unit of the neurology department, and the indoor environment was maintained at a constant temperature and humidity. Ag/AgCl electrodes were placed according to the international 10 to 20 system. The impedance of each electrode was maintained below 5 kΩ, the sampling rate was 500 HZ, and the filtering range was 0.5 to 70 Hz. Data were stored in the European Data Format.

2.2..2. Quantitative EEG parameters extraction. Selected continuous EEG data with a length of about 30 minutes without artifacts were analyzed quantitatively with the MATLAB R2015a (The MathWorks, Inc. MA) software and its EEGLAB toolbox. The following steps were performed: preprocessing: 50 Hz notch filtering was performed to remove power frequency interference; the third-order Butterworth filter was selected as the high-pass filter, the −3 dB cutoff the frequency was 1 Hz; the 8th order Butterworth filter was selected as the low-pass filter selects, and the −3 dB cutoff frequency is 30 Hz; adaptive noise reduction: eye electrical interference was removed by using the method provided by the EEGLAB toolbox. And ICA noise reduction processing was then conducted; each piece of EEG data was cut into 4 s epoch for power spectral density analysis, the Welch method was used as the algorithm, the window length was 4 s, and overlap was 50%. BSI was calculated in the frequency range 1 to 7 Hz (BSIslow) and 7 to 25 Hz (BSIfast).[11] BSI was also calculated in each electrodes pair. Additional details are presented in Appendix Supplemental Digital Content, http://links.lww.com/MD/H845.

2.2..3. Neuroradiology. The CT scans were performed within 3 days after onset, using a Philips Brilliance machine (Philips, Amsterdam, Netherlands) and MedViewer software, with a thickness of 5 mm. During the detection, the lesion area was manually outlined layer by layer, and the volume was calculated as the sum of the total lesion area multiplied by the layer thickness and the layer spacing. The midline shift was measured at the septum pellucidum level.

2.3. Outcomes

The 3-month mortality of the patients was taken as the outcome.

2.4. Statistical analysis

SPSS statistical software (version 26.0, SPSS Institute, Inc., Chicago, IL) was used for data analysis. The measurement data for normal distribution were expressed as mean ± standard deviation and compared using the *t* test. The skew distribution data was represented by median and quartile spacing, and a rank-sum test was used for comparison between groups. Counting data was represented by frequency and compared using the Chi-square test. A multivariable logistic regression model was constructed to evaluate the independent predictive ability of outcome predictors. Due to the possible correlation between different BSI parameters, we selected stepwise regression approaches. BSI is a ratio and all less than 1, in order to better explain the meaning of OR value, we enlarge the BSI by 100 times for calculation when conducting binary logistics regression. Receiver operating characteristic analysis and calculation of the Youden index were used to identify the optimal cutoff point to best predicted the 3-month mortality. To enhance the diagnostic efficiency, logistic regression analyses were used to construct a diagnostic model using the common risk factors and BSI. The significance level was set at $P < .05$.

3. Results

3.1. Baseline characteristics

A total of 38 LHI patients (25 males and 13 females) were included with an average age of 66 years. There were 23 cases in the survival group and 15 cases in the mortality group. All baseline data were listed in Table 1. The Glasgow Coma Scale (GCS) and National Institute of Health stroke scale on admission was 8 (5,11) and 18 (14,23), 65.8% patients had left infarction. The time between onset to the first monitoring was 22.9 (8.6,49.4) hours. The GCS score on admission was significantly higher in the survival group than that in the mortality group (10[7,12] vs. 6[5,8], $P = .018$). The infarct volume was significantly larger in the mortality group than that in the survival group (347.0 vs. 487.3, $P = .036$). No other baseline characteristics were found significantly different between the 2 groups.

3.2. Differences in BSI parameters between survival and mortality groups

Among all the BSI parameters, significantly higher BSIfastC3–C4, BSIslowC3–C4, and BSIslowO1–O2 were observed in mortality group than that in survival group at 3 months (0.02[0.00,0.06] vs. 0.24[0.07,0.21], $P = .001$; 0.04[0.02,0.07] vs. 0.22[0.03,0.39], $P = .010$; 0.02[0.02,0.15] vs. 0.12[0.04,0.32], $P = .009$). Other BSI parameters were of no difference (Table 2).

3.3. Multivariable analysis

We puted GCS on admission, infarct volume, BSIfastC3–C4, BSIslowC3–C4, and BSIslowO1–O2 into the multivariable logistic regression model. Only BSIfastC3–C4(adjusted OR = 1.059, 95% CI 1.003,1.119, $P = .039$) was independent factor in prediction of 3-month mortality (Table 3).

Table 1

Baseline characteristics of study patients.

Characteristic	Total (*n* = 38)	Survival group (*n* = 23)	Mortality group (*n* = 15)	*P* value
Age, yr, **m**ean ± SD	66 ± 11	63 ± 10	70 ± 11	.057
Male, *n* (%)	25 (65.8)	16(69.6)	9 (60.0)	.544
Admission NIHSS, median (IQR)	18 (14,23)	18 (13,23)	21 (17,23)	.119
Admission GCS, median (IQR)	8 (5,11)	10 (7,12)	6(5,8)	**.018**
Previous medical history, n (%)				
Hypertension	26 (68.4)	15 (65.2)	11(73.3)	.599
Atrial fibrillation	11 (28.9)	5 (21.7)	6 (40.0)	.225
Diabetes	11 (29.0)	5 (22.0)	6 (40.0)	.225
Complication, *n* (%)				
Pneumonia	30(79.0)	19 (82.7)	11(73.3)	.493
AGML	17 (44.7)	12 (52.2)	5 (33.3)	.254
DVT	9 (23.7)	5 (21.7)	4 (26.7)	.727
Baseline imaging parameters				
Left side lesion, *n* (%)	25 (65.8)	14 (60.9)	11 (73.3)	.429
Infarct volume, ml, Mean ± SD	395.2 ± 181.7	347.0 ± 150.5	487.3 ± 206.9	**.036**
The midline shift (mm), median (IQR)	2.55(0, 7.02)	2.39 (0,5.94)	2.8 (0,8.00)	.352
EEG monitoring				
Time from onset to the first monitoring (h), median (IQR)	22.9 (8.6,49.4)	36.0 (4.0,62.3)	22.0 (10.1,42.4)	.521

AGML = acute gastric mucosal lesions, DVT = deep vein thrombosis of the lower extremity, EEG = electroencephalography, GCS = Glasgow Coma Scale, IQR = interquartile range, NIHSS = National Institute of Health stroke scale.

Table 2

Analysis of BSI for predicting 3-month nonsurvival outcome.

QEEG parameters	Electrodes pair	Survival group (*n* = 23)	Mortality group (*n* = 15)	*P* value
BSIfast	Fp1–Fp2	0.01 (0.00,0.10)	0.01 (0.04,0.04)	.134
	F3–F4	0.06 (0.03,0.12)	0.05 (0.03,0.17)	.478
	F7–F8	0.08 (0.02,0.11)	0.05 (0.00,0.14)	.517
	C3–C4	0.02 (0.00,0.06)	0.24 (0.07,0.43)	**.001**
	T3–T4	0.09 (0.02,0.14)	0.08 (0.01,0.21)	.684
	P3–P4	0.08 (0.10,0.18)	0.12 (0.07,0.21)	.335
	T5–T6	0.05 (0.10,0.17)	0.17 (0.05,0.36)	.059
	O1–O2	0.08 (0.02,0.15)	0.15 (0.09,0.22)	.198
BSIslow	Fp1–Fp2	0.05 (0.01,0.15)	0.06 (0.0,0.14)	.890
	F3–F4	0.08 (0.02,0.11)	0.11 (0.03,0.20)	.219
	F7–F8	0.06 (0.03,0.14)	0.09 (0.01,0.15)	.503
	C3–C4	0.04 (0.02,0.07)	0.22 (0.03,0.39)	**.010**
	T3–T4	0.11 (0.06,0.20)	0.11 (0.03,0.15)	.238
	P3–P4	0.07 (0.03,0.10)	0.14 (0.06,0.24)	.152
	T5–T6	0.04 (0.02,0.12)	0.07 (0.01,0.26)	.186
	O1–O2	0.02 (0.02,0.15)	0.12 (0.04,0.32)	**.009**

BSI = brain symmetry index, QEEG = quantitative electroencephalography.

Table 3

Multinomial logistics regression analysis: effect of different variables on 3-month mortality.

Variables	*P* value	OR (95%CI)
BSIfastC3–C4	**.039**	1.059 (1.003–1.119)
BSIslowO1–O2	.075	1.056 (0.995–1.120)

BSI = brain symmetry index, CI = confidence interval, OR = odds ratio.

3.4. Accuracy analysis of predicting outcomes

The receiver operating characteristic curves of BSIfastC3–C4, GCS and infarct volume to predict 3-month mortality were shown in Fig. 1. The sensitivity, specificity, and area under curve (AUC) were shown in Table 4. The results indicate that only the BSIfastC3–C4 had a significantly diagnostic value to predict 3-month outcome (AUC = 0.805, *P* = .005). To enhance the diagnostic efficiency, logistic regression analyses were used to construct diagnostic models using BSIfastC3–C4, GCS and infarct volume. The combination marker had a higher diagnostic value than BSIfastC3–C4(AUC = 0.840, *P* = .002).

4. Discussion

Treatment of LHI has been a major unsolved problem in neurocritical care, with a high mortality rate and the disease progresses rapidly. To judge the prognosis of the disease as soon as possible could help to guide the follow-up treatment. At present, the commonly used indicators in clinical are GCS and imaging indicators. However, the accuracy of the GCS evaluation is impaired by the strong subjectivity of physicians as well as the fact that the speaking evaluation is susceptible to aphasia, intubation and mechanical ventilation.[12] The acquisition of imaging indicators also requires patients to visit the department of radiology, which may have a potential risk of aggravating the patient's condition. However, bedside noninvasive QEEG overcomes these shortcomings.

In our study, we found that early BSIfastC3–C4 can predict the 3-month mortality of LHI patients. BSIfastC3–C4 was an independent predictor of GCS and infarct volume. And it has high diagnostic value (AUC = 0.805, *P* = .005). And our study is the first study to propose that a combination marker of early infarct volume, GCS, and QEEG parameters to predict prognosis, which is all clinically easily available parameters.

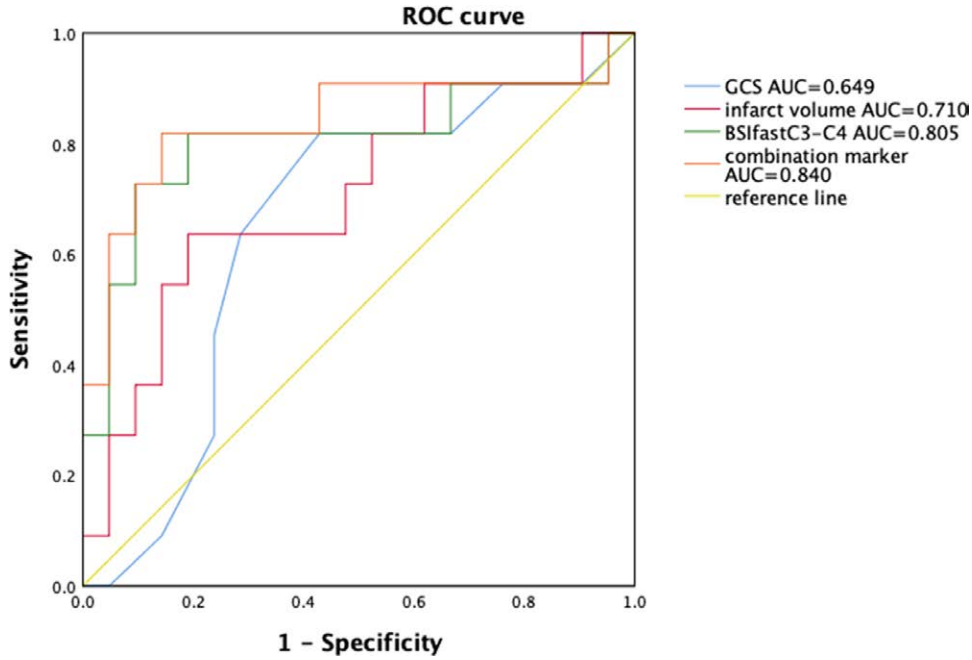

Figure 1. ROC curves of BSIfastC3–C4, GCS, infarct volume and combination maker for predicting 3-month mortality. AUC: area under curve, BSI: brain symmetry index, ROC curve: receiver operating characteristic curve, GCS: Glasgow Coma Scale.

Table 4

The diagnosis results of the variables.

Variables	AUC	Sensitivity	Specificity	cutoff value	P value
BSIfastC3-C4	0.805	0.727	0.905	0.132	**0.005**
GCS	0.649	0.818	0.571	9	0.171
Infarct volume	0.710	0.636	0.810	464.1	0.054
Combination marker	0.840	0.818	0.857	-2.271	**0.002**

AUC = area under curve, BSI = brain symmetry index, GCS = Glasgow Coma Scale.

The diagnostic value of the combination marker is higher. (AUC = 0.840, *P* = .002).

BSI was first used during carotid surgery as a reliable method to detect early brain ischemia. In recent years, a statistically significant difference was observed in BSI between stroke patients and the matched healthy controls.[13,14] Higher BSI values reflect more power asymmetry over the cerebral hemispheres and predict more upper limb motor impairment 6 months after stroke.[15,16] So BSI can serve as a prognostic biomarker of stroke recovery. BSI can also be used to assess the neurorehabilitative effect.[17,18] However, none of these studies focus on the LHI population, which has a large infarct volume and is more likely to get intracranial hypertension.

In our study, we calculated the BSI for each electrode pair in the hope of calculating a better predictor with a smaller number of electrodes. Our results showed that BSIfastC3–C4 is valuable in predicting 3-month mortality, with a specificity of 90.5% and a large area under the curve. According to the inclusion criteria, the heterogeneity of the included patients at the infarct site was small, which affecting the entire or total subterritory of the middle cerebral artery.[19] That is the significance to study the effects of different electrodes on BSI. Since the entire or total subterritory of the middle cerebral artery were affected, the temporal lobe would be the most damaged, while the occipital lobe and the frontal lobe are also mostly damaged due to huge cerebral edema. The EEG activity in the parietal lobe may be the breakthrough point to distinguish the survival and mortality groups. Our results support this hypothesis since the C3–C4 electrodes are right in the parietal lobe. This may suggest that in the future QEEG prognostic studies for LHI could focus more on the location of the parietal lobe or the midline, and perhaps could predict the prognosis of LHI with fewer electrodes.

As can be seen from Table 2, both BSIfast and BSIslow had significant differences at electrode pairs between the 2 groups, but only BSIfastC3–C4 reached the statistical significance of independently affecting the prognosis. Due to our small sample size, we cannot conclude that BSIfast may be more valuable than BSIslow. However, our results indicate that BSI is a promising predictor of 3-month prognosis for LHI.

This study is a prospective study to evaluate the prognosis of BSI in patients with LHI. We think our data are true and reliable. We try our best to get rid of the confounding factors that may confuse the results. We try to reduce the increase in slow-wave activity caused by sweating and blinking. There are some limitations in this study: The group was limited in the number of patients; a larger group of patients would probably have strengthened the results. Our study did not set a secondary outcome to more fully reflect the clinical value of BSI. However, despite these limitations, we successfully identified BSIfastC3–C4 as a predictor for 3-month mortality in patients with LHI. Our results indicate that BSI is a promising predictor of prognosis for LHI. In the future, we need more studies to focus on that.

5. Conclusions

Our results demonstrate that BSIfastC3–C4 has the ability to independently predict the prognosis of LHI at 3 months. At the same time, the combination marker which includes GCS, infarct volume

and BSIfastC3–C4 has a better diagnostic value. Additionally, it is imperative to confirm these findings through large-scale trials.

Author Contributions

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