

The change index of quantitative electroencephalography for evaluating the prognosis of large hemispheric infarction

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A growing number of studies have demonstrated the role of quantitative electroencephalography in assessing brain function in neuro-intensive care units. Still, few studies have examined patients with large hemisphere infarction. Thirty patients with large hemisphere infarction were included in this preliminary study, and the patients were divided into the death group (twelve patients) and survival group (eighteen patients). Electroencephalography monitored the patients, and a computerized tomography inspection was performed. The quantitative electroencephalography of the alpha-beta/delta-theta ratio change index was calculated and used to predict the prognosis of early large hemisphere infarction patients. The relationship between three months modified Rankin Scale, and alpha-beta/delta-theta ratio change index was analyzed. The death group had negative changes for alpha-beta/delta-theta ratio change index (-0.0140 ± 0.0193), while there was an opposite trend in the survival group, the median is 0.004 ($-0.0067, 0.0137$). The death group's brain function decreased more severely and rapidly than the survival group ($P = 0.004$). The highest diagnostic value (AUC value $0.815, P < 0.001$) was observed when the alpha-beta/delta-theta ratio change index dropped and exceeded -0.008 . The area under the GCS curve was 0.674 , but its predictive ability was low ($P = 0.094$). The correlation analysis result showed that the 3-month modified Rankin Scale was negatively correlated with the alpha-beta/delta-theta ratio change index ($r = -0.489, P = 0.006$). The alpha-beta/delta-theta ratio change index is considered an indicator for predicting the prognosis of large hemisphere infarction. Therefore, the alpha-beta/delta-theta ratio change index may be a reliable quantitative EEG parameter that predicts the early prognosis of patients with acute large hemispheric infarction.

Keywords

Large hemispheric infarction; Acute phase; Alpha-beta/delta-theta ratio; Change index; Quantitative electroencephalogram; Prognosis

1. Introduction

Large hemispheric infarction (LHI) is an ischemic stroke affecting the entire or total sub-territory of the middle cerebral artery, involving the basal ganglia at least partially, with or without the adjacent territories' involvement [1]. It con-

tinues to be associated with significant mortality and morbidity, and patients with LHI have a poor prognosis. Therefore, LHI is also known as malignant middle cerebral artery infarction (MCHI) [2], and its incidence accounts for about 5%–10% of all ischemic strokes [3].

As an examination technique of brain bioelectric activity, electroencephalography can directly reflect the abnormal state of brain function and metabolism. It is more sensitive to brain damage caused by the reduction of cerebral blood flow, and its sensitivity is higher than computerized tomography (CT) and other imaging examinations [4]. Quantitative EEG (QEEG) is a quantitative analysis method based on primitive EEG, which is currently widely used in mental diseases, epilepsy, traumatic brain injury, cerebrovascular diseases, Parkinson's disease, cognitive related, sleep, and many pain diseases. The advantage of QEEG is that it abandons the disadvantage of high requirements of the original EEG on judging readers. The computer generates data, and the result is more objective and reliable. Clinical studies have revealed that QEEG parameters change earlier than clinical indicators, and its predictive value is higher than imaging data and clinical scales [5–7]. Several studies have shown that higher delta power, lower-alpha power and beta power are reliable QEEG indicators for poor prognosis in patients with acute ischemic stroke (IS) [5, 7–9]. Studies also indicated that the ratio of delta-theta to alpha-beta (DTABR) and DAR indicators have a high prognostic ability for IS patients [6, 7, 10].

However, studies about QEEG in early LHI are limited. Only two case-report studies revealed that an increase of delta power in the opposite hemisphere suggests a poor prognosis [11], and [12] found that theta power is meaningful in predicting the outcome of death in patients with LHI and is superior to visual EEG and Glasgow Coma Scale (GCS). Alpha-beta/delta-theta ratio (ABDTR) is positively correlated with the patients' prognosis. The authors in [8] have correlated ischemic cortical stroke patients' clinical outcomes with acute QEEG, DWI, and PWI data and verified that the 30-day Na-

tional Institute of Health Stroke Scale (NIHSS) had equivalent correlations with ADCI (acute delta change index) and MTT abnormality volume, both were more significant than the correlation between acute DWI lesion volume and 30-day NIHSS.

2. Materials and methods

2.1 Study object

The detailed information of LHI patients confirmed by head CT or MR in the Intensive Care Unit (ICU) of the Second Affiliated Hospital of Hebei Medical University from August 2017 to July 2020 was collected. This study was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Hebei Medical University. All patients were managed following Evidence-Based Guidelines for the Management of LHI [1]. This study was registered at the China Clinical Trial Center, the review resolution number was 2017-P018, and the registration number was ChiCTR1800016468.

2.2 Collection of primary patient data

Collect the patients baseline clinical and diagnostic data, such as age, gender, risk factors, complication [Lung infection, Acute Gastric Mucosal Lesions, deep vein thrombosis of the lower extremity, and the cerebral hernia], GCS and NIHSS on admission, ICU hospital stay (day), imaging indicator [infarct side and volume, the midline shift of septum pellucidum, the midline shift of pineal gland], EEG monitoring [the time from the first monitoring to the onset (h), the time interval between two EEGs (h)], and the mRS of 3 months. A cerebral hernia is defined as cerebral edema whose clinical manifestations are unequal pupils, head imaging manifests as a mass effect, and midline displacement ≥ 5 mm, all of which are simultaneously available. The patients were divided into survival and death groups by taking the patient's three months' survival as the leading endpoint, and the three months' modified Rankin Scale (mRS) score was recorded.

2.3 Inclusion and exclusion criteria

Inclusion criteria: (1) Patients older than 18 years; (2) Patients who received ICU treatment within three days of onset; (3) CT or MRI confirmed that more than 2/3 area of the middle cerebral artery blood supply area was involved, with or without infarction of the anterior and posterior cerebral arteries; (4) The informed consent form was signed by the patient's family member or guardian; (5) Patients with reduced levels of consciousness, and the NIHSS scores were higher than 14 (in patients with an infarction in the non-dominant hemisphere) or higher than 19 (in patients with an infarction in the dominant hemisphere). Exclusion criteria: (1) Patients with multiple infarctions of the cerebellum, brain stem, or bilateral cerebral hemispheres; (2) Patients who received antiepileptic drugs or sedative drugs within 24 hours before EEG monitoring, which may affect brain electrical activity; (3) Patient's pre-onset mRS score ≥ 2 points; (4) Patients who had significant diseases that may seriously affect the prognosis,

such as severe heart failure at the time of onset; (5) Patients who had severe interference that made the EEG unreadable; (6) Estimated death within 48 h; (7) Hemorrhages or other associated brain lesions; (8) heart arrest; (9) The absence of pupillary reflexes.

2.4 Experimental method

2.4.1 EEG monitoring

The patients were monitored by using the digital EEG machine (Model Neusen. U) of Boruikang Technology (Changzhou) Co., Ltd within three days of onset, 2 hours each time, and at least two times for each case; the monitoring was performed in the ICU of the neurology department, and the indoor environment was maintained at a constant temperature and humidity [6]. Since standard clinical EEG arrays are sufficient for post-stroke monitoring and prognosis, high-density electrode arrays are unnecessary. The international 10–20 method was adopted for electrode placement, and the international standard 19-lead EEG was connected, including, Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, P3, P4, O1, and O2. The silver disk electrode was used as the recording electrode (Cz, A1, A2 points are reference electrodes; Fpz points are ground electrodes). Each lead's resistance was controlled within 5,000 ohms, the sampling rate was 1000 Hz, and the filtering range was 0.053–500 Hz. Clinicians had no access to the patient's EEG data during the diagnosis and treatment, and the data was stored in the form of European Data Format (EDF) files.

2.4.2 QEEG parameter extraction

MATLAB (MATLAB R2015a, The MathWorks, Inc. MA, USA) software and its EEGLAB toolbox were used for quantitative analysis. Two measured EEGs within four days of onset were selected, and the EEG index was calculated. For each monitoring, continuous EEG data with a length of about 30 minutes without motion interference were chosen, and the following steps were performed: (1) Preprocessing: power frequency interference was removed by performing 50 Hz notch filtering; the third-order Butterworth filter was selected as the high-pass filter, the -3dB cutoff frequency was 1 Hz; the 8th order Butterworth filter was selected as the low-pass filter, and the -3dB cutoff frequency was 30 Hz. (2) Adaptive noise reduction: eye electrical interference removal and ICA noise reduction processing were performed using the EEGLAB toolbox method. (3) Each piece of EEG data was cut into 2 s epoch for power spectral density analysis, the Welch method was adapted as an algorithm, window length was 2 s, and overlap was 50%. The ABDTR was calculated, the average value of each epoch's ratio, the band power Alpha, Beta to band power Delta and Theta, namely $(PA + PB)/(PD + PT)$, the frequency range of each band were shown in Table 1. After calculating the ABDTR of each electrode, the average number of all electrodes was considered the average scalp ABDTR. The ABDTR index was calculated by the second ABDTR of EEG monitoring minus the first ABDTR, divided by the first ABDTR value and the intervals (h) [8]. The

Table 1. Quantitative EEG parameters.

EEG parameters	Abbreviation	Frequency range
Total power	-	1–30 Hz
Delta power	-	1–4 Hz
Theta power	-	4–8 Hz
Alpha power	-	8–12.5 Hz
Beta power	-	12.5–30 Hz
Alpha-beta/delta-theta	ABDTR	8–30/1–8 Hz

ABDTR change index reflects not only the direction but also the degree of EEG changes. In this study, we used ABDTR and its change index to measure brain function.

2.4.3 CT inspection

CT inspection was performed using the Philips Brilliance CT model, the layer thickness and the layer spacing were both 10 mm, and the measurement software was MedViewer. During the detection, the lesion area was manually outlined layer by layer. The volume was calculated as the sum of the total lesion area multiplied by the layer thickness and the layer spacing. The midline displacement distance was measured at the septum pellucidum level and the pineal gland level, respectively. The head CT results of the patients with the enormous infarct volume during hospitalization were included in the fundamental data analysis.

2.5 Statistical analysis

SPSS 22.0 was used for data analysis. The measurement data conforming to the normal distribution were expressed as mean \pm standard deviation and compared using the *t*-test. The measurement data that does not conform to the normal distribution was represented by median and quartile spacing, and the rank-sum test was used to compare groups. Counting data was represented by frequency or percentage and compared using the chi-square test. The Pearson correlation coefficient was used for the correlation detection of data conforming to the normal distribution, and the Spearman correlation coefficient was used for the correlation detection of the non-normal distribution data. ROC curves were plotted to determine the critical value of the data index. The quantitative EEG threshold was calculated, and the sensitivity and specificity of the prognosis were evaluated. Set the inspection level α to 0.05, $P < 0.05$ indicates that the difference is statistically significant.

3. Results

3.1 Baseline information

A total of 30 patients (20 males and 10 females) with LHI were included in this study, with an average age of 67.27 ± 9.94 . There were 18 cases (60.00%) in the survival group and 12 cases (40.00%) in the death group. All baseline data were listed in Table 2. The GCS at admission was 6.73 ± 3.05 , 18 patients (60.00%) had left infarction, and 14 patients (46.67%) had a cerebral hernia. The first monitoring to the onset was 29.99 (22.36, 53.22) hours, and the time interval between the

two EEGs was 20.83 ± 14.42 hours. There were no significant differences between the two groups regarding age, gender, GCS and NIHSS at admission, side of infarction, the time interval between two EEGs, coronary heart disease (CHD), and other indicators.

3.2 Differences in ABDTR change index between death and survival groups

In terms of the change index of ABDTR, a more severe and rapid brain function decline was noticed in the death group (-0.0140 ± 0.0193) compared with the survival group [$0.004 (-0.0067, 0.0137)$], Mann-Whitney test results showed that the two groups were statistically different ($Z = -2.879$, $P = 0.004$).

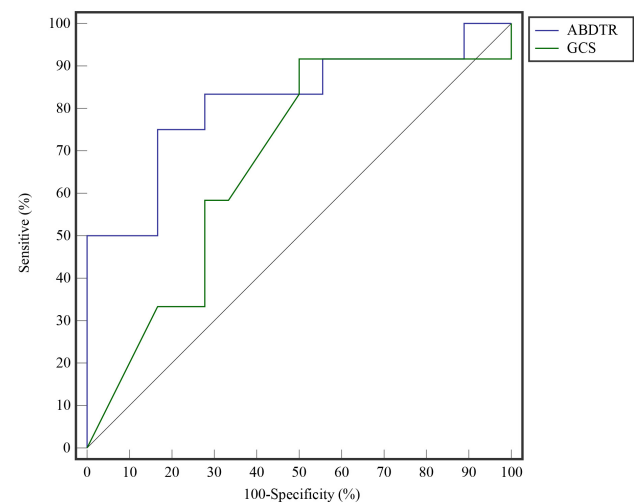


Fig. 1. The ROC Curve of the ABDTR change index and Glasgow Coma Scale (GCS).

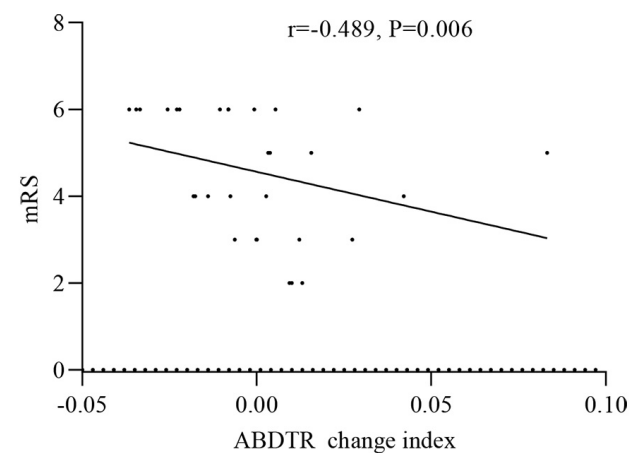


Fig. 2. The correlation between the ABDTR change index and the 3-month mRS detection.

Table 2. General information on patients with large hemispheric infarction.

Projects	Total	Survival group	Death group	<i>P</i>
	(n = 30, %)	(n = 18, %)	(n = 12, %)	
Basic information				
Age (year)	67.27 ± 9.94	65.72 ± 10.67	69.58 ± 8.65	0.310
Gender (Male, %)	20 (66.67)	12 (66.67)	8 (66.67)	1.000
Risk factors				
Hypertension	18 (60.00)	11 (61.11)	7 (58.33)	1.000
Atrial fibrillation	14 (46.67)	6 (33.33)	8 (66.67)	0.073
Ischemic stroke	8 (26.67)	3 (16.67)	5 (41.67)	0.210
CHD	12 (40.00)	5 (27.78)	7 (58.33)	0.196
Diabetes	7 (23.33)	3 (16.67)	4 (33.33)	0.392
Complication				
Brain herniation	14 (46.67)	6 (33.33)	8 (66.67)	0.073
Lung infection	25 (83.33)	15 (83.33)	10 (83.33)	1.000
AGML	18 (60.00)	13 (72.22)	5 (41.67)	0.136
DVT	6 (20.00)	3 (16.67)	3 (25.00)	0.660
GCS on admission	6.73 ± 3.05	8.00 (4.00, 9.25)	5.83 ± 3.16	0.108
NIHSS on admission	22.52 ± 6.30	20.29 ± 4.61	25.67 ± 7.10	0.056
ICU hospital stay (Day)	24.00 (21.75, 28.50)	24 (20.75, 25.00)	28.92 ± 10.69	0.212
Imaging indicator				
Infarct site (Left)	18 (60.00)	13 (72.22)	7 (58.33)	0.461
Infarct volume	400.69 ± 213.73	331.77 ± 166.61	504.09 ± 241.03	0.119
The midline shift of septum pellucidum	6.00 ± 5.15	5.29 ± 4.23	7.07 ± 6.34	0.051
The midline shift of pineal gland	4.19 ± 3.79	3.86 ± 3.20	4.69 ± 4.65	0.097
EEG monitoring				
The time from the first monitoring to the onset (h)	29.99 (22.36, 53.22)	29.95 (21.25, 46.58)	39.39 ± 23.72	0.932
The time interval between two EEGs (h)	20.83 ± 14.42	22.22 ± 14.75	18.82 ± 14.39	0.813

The measurement data conform to the normal distribution and uses the Mean ± Standard Deviation. The *t*-test is used to compare groups; the median and quartile interval are used for non-conformity distribution, and the rank-sum test is used to compare groups. Counting data is expressed by frequency and percentage, and the chi-square test is used for comparison between groups. CHD, Coronary Heart Disease; AGML, Acute Gastric Mucosal Lesions; DVT, Deep vein thrombosis of the lower extremity.

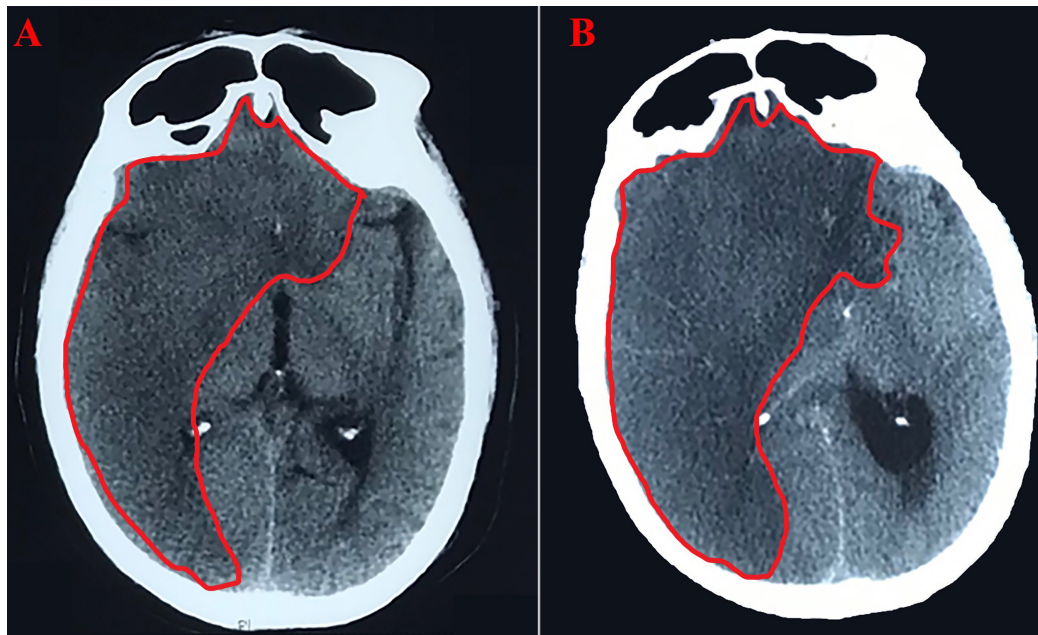
**Fig. 3. The CT results of typical cases.** (A) Onset 23 h CT scan. (B) Onset 43 h CT scan. The red line is the lesion.

Table 3. The diagnosis results of GCS and ABDTR change index.

Factor	AUC	95% CI	Sensitivity (%)	Specificity (%)	Youden	Related Standards	Z	P
GCS	0.674	0.479–0.833	91.67	50.00	0.417	≤8	1.675	0.094
ABDTR change index	0.815	0.631–0.932	75.00	83.33	0.5833	≤-0.008	3.552	<0.001

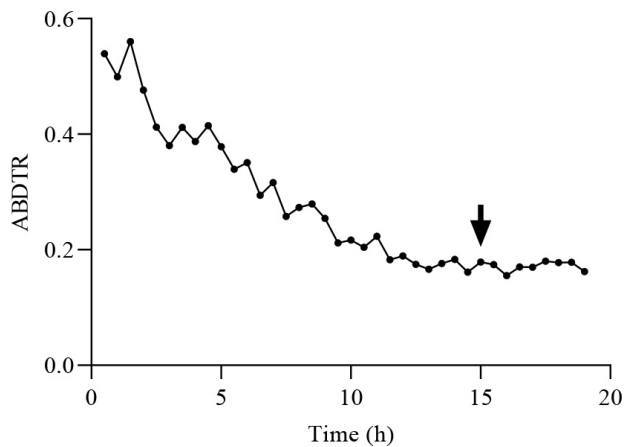


Fig. 4. The typical cases of ABDTR result in continuous long-term monitoring after 24 hours of onset. Down arrow: the time when the pupil size of both eyes was not equal.

3.3 The sensitivity and specificity of ABDTR change index to predict the prognosis of LHI

The ABDTR change index diagnostic results showed that the area under the curve, sensitivity, specificity, and the Youden index was 0.815, 75.00%, 83.33%, and 58.33%, respectively ($Z = 3.552$, $P < 0.001$, Fig. 1). The highest diagnostic value of the ABDTR change index was obtained when the change index dropped and exceeded -0.008. The area under the GCS curve was 0.674, and the predictive ability of GCS was low ($Z = 1.675$, $P = 0.094$). It can be concluded that the ABDTR change index's diagnostic value was higher than the GCS curve (Fig. 1, Table 3).

3.4 Correlation analysis of ABDTR change index and 3-month mRS detection

According to the correlation analysis results, the 3-month mRS was significantly negatively correlated with ABDTR change index ($r = -0.489$, $P = 0.006$) (Fig. 2).

3.5 Typical cases

Typical patient: A 79-years-old male with a previous history of hypertension, diabetes, and coronary heart disease was admitted to our hospital. A specific dose of rtPa (0.9 mg/kg) for thrombolysis was given 46 minutes 2 hours after onset, 5 points for GCS on admission, and 30 points for NIHSS. The head CT at 23 h after the onset was shown in Fig. 3, and continuous long-term monitoring was started 24 h after the onset. Every half hour, a constant 10 minutes of non-interfering EEG data was taken as the characteristics of the half-hour period. The ABDTR was calculated, and the line chart was generated as above. Thirty-nine hours after the onset (the 15 h point), the pupils were unequal in size.

The patient's right pupil diameter was 6.0 mm, and the light reflection disappeared; the left pupil diameter was 3 mm, and the light reflection was dull, and his vital signs were stable. About 4 hours later, the head CT was re-checked and was shown in the figure. Because the patient went out for a head CT examination, the EEG monitoring was stopped. The total duration of the EEG monitoring was 18.5 hours. It can be seen that the patient's ABDTR has continued to decline before the clinical change (Fig. 4).

4. Discussion

This study showed that the ABDTR change index was significantly different between the death and survival groups ($P = 0.004$). Using the ABDTR change index as a diagnostic indicator, the AUC, sensitivity and specificity were 0.815, 75.00%, 83.33%, respectively. The results illustrated that the ABDTR change index has a higher predicted diagnostic value than the value of GCS. Simultaneously, there was also a significant correlation between the ABDTR change index and the 3-month mRS score ($P < 0.05$).

EEG is mainly caused by excitatory and inhibitory postsynaptic currents in the dendrites of cortical pyramidal cells and is very sensitive to detect cerebral ischemia. Ischemic stroke can have various abnormal typical manifestations on an electroencephalogram. Whole-brain delta (absolute) power often changes significantly over time, depending on the severity and evolution of stroke [8]. At moderate ischemic levels, before the delta frequency appears, beta (usually 14–30 Hz) attenuation may also occur [13], followed by slower alpha (typically 8–13 Hz) activity [14].

Some evidence from joint EEG and neuroimaging observations and animal studies indicate that alpha activity disorders (e.g., amplitude attenuation, slowing) usually indicate cortical damage, while abnormal delta frequencies reflect subcortical and/or white matter damage the cortex goes in [15, 16]. However, this is just a conjecture, and we need more evidence to assess these possibilities finally. Of the 20 QEEG measurements calculated using Fourier transform or other analysis, the delta power measurement has the strongest negative correlation with regional cerebral blood flow (rCBF). Other evidence suggests that the delta frequency may reflect pathophysiological processes such as oxidative stress [17].

There are very few quantitative EEG studies on LHI. Finnigan SP *et al.* [11] found that the contralateral hemisphere delta power can be a predictor of poor prognosis. The authors in [12] found that the contralateral hemisphere's theta power can predict poor prognosis, but the diagnostic value is moderate. They speculated that the mix of delta activity and artifacts resembling delta activity eliminated the sig-

nificant difference in delta power and affected the analysis of DTABR, which also involves delta power. Therefore, they suggested that more attention should be paid to theta power in the quantitative EEG study of LHI. A study suggests that theta power may be related to patients with cerebral edema.

The authors in [9] found that theta power is the best predictor of short-term results (along with alpha power) because it is related to dysfunctional but still viable tissues, which may be related to the ischemic penumbra or edema area. In this study, we believe that theta power detection has definite clinical significance in LHI patients. LHI has a larger infarct core and a larger edema volume compared with patients with mild cerebral infarction.

According to previous studies, we think that the power of delta, theta, beta, and alpha may all have significance in developing LHI disease. Therefore, the ABDTR change index was selected, and it includes multiple power indicators that may affect the prognosis, which can improve the diagnostic value. As a prospective study, this study minimizes various artifacts during EEG monitoring implementation, ensuring the quality of EEG monitoring and high diagnostic value.

Other research results suggest that theta and beta frequencies are unreliable in pathophysiology after stroke as delta and alpha frequencies [5, 10, 13, 18, 19]. It may be because these studies excluded cases with a GCS of fewer than 6 points, and the included population had a small infarct size and did not produce large-scale cerebral edema. Therefore, the results of these trials do not apply to the diagnosis and research of LHI.

In early LHI patients, especially within three days, the predictive value of various parameters is not high, such as imaging indicators, multiple scores, and original EEG monitoring. There may be different clinical outcomes in the same infarct volume because of the influence of numerous factors, such as age, degree of brain atrophy, and systemic stress response. EEG monitoring is sensitive to time changes. We used time parameters and the ABDTR change index, obtained from two EEG monitoring indicators to evaluate the prognosis. This indicator can reflect the degree of brain function change and the direction of change. Many studies have proved the prognostic significance of GCS, NIHSS, and infarct volume for LHI [20–23]. Our study showed no statistically significant difference between GCS and NIHSS in the survival and death groups. The ABDTR change index is statistically different between the two groups, and the diagnostic effect of this index is also better than that of GCS and NIHSS. Therefore, we believe that the ABDTR change index has good value in the LHI forecasting process. The NIHSS score is limited in patients with aphasia and coma, so this article did not use the NIHSS score but used the GCS score. We demonstrated that the ABDTR change index is more valuable than GCS diagnosing of death through our experiment.

Computer-aided EEG interpretation systems have shown the potential to enhance non-expert recognition of many EEG abnormalities in adult neurologically critical patients [24]. Therefore, the extraction of specific EEG param-

eters for specific diseases will provide great help for the clinical monitoring of nerve functions at the bedside to detect changes in the patient's condition and guide clinical treatment. We found that ABDTR may also become a valuable indicator in long-range EEG monitoring by presenting a typical case.

Our findings are based on the small size of the population. There are twofold reasons for the small sample size: First, there are relatively few patients with LHI; Second, this is preliminary research with limited experimental personnel and experimental time. Another limitation is that the interval between two EEGs was not uniform. However, we improved through the test method. We have used dividing by the time interval to minimize the interference caused by different time intervals. Therefore, multi-center clinical trials are required in the future to verify the results of this trial.

5. Conclusions

This experiment demonstrates that the ABDTR change index may be a valuable indicator for predicting the prognosis of LHI. A multi-center clinical trial is required in the future to verify the results of this trial.

Abbreviations

ABDTR, alpha-beta/delta-theta ratio; ADCI, acute delta change index; CHD, coronary heart disease; DTABR, ratio of delta-theta to alpha-beta; EDF, European Data Format; GCS, Glasgow Coma Scale; ICU, Intensive Care Unit; IS, ischemic stroke; LHI, large hemispheric infarction; MCHI, middle cerebral artery infarction; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; QEEG, quantitative electroencephalography; rCBF, regional cerebral blood flow.

Author contributions

JT, LG and LDL conceived and designed the study. YZ and ZZ performed data acquisition. YHP and DCL analyzed the data. JT and LG wrote the paper. All authors approved the final article.

Ethics approval and consent to participate

This study was obtained with the informed consent of all participants. The institutional review board of the Ethics Committee of the Second Affiliated Hospital of Hebei Medical University approved this study, code 2017-P018.

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Conflict of interest

The authors declare no conflict of interest.

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