Original Article

Evaluation of cerebral function in high risk term infants by using a scoring system based on aEEG

Fang Luo, Zheng Chen, Huijia Lin, Chenhong Wang, Xiaolu Ma, Liping Shi

Department of Neonatal Intensive Care Unit, The Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

Contributions: (I) Conception and design: F Luo; (II) Administrative support: None; (III) Provision of study materials or patients: Z Chen, H Lin, C Wang, X Ma; (IV) Collection and assembly of data: L Shi; (V) Data analysis and interpretation: L Shi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Fang Luo. Department of Neonatal Intensive Care Unit, Children's Hospital of Zhejiang University School of Medicine, 57 Zhugangxiang, Yan'an Road, Hangzhou 310003, China. Email: csuanna@163.com.

Objective: To investigate the relationship between the amplitude integrated electroencephalogram (aEEG) findings and neurodevelopmental outcomes of high-risk term infants with neurological disorders and develop a scoring system for assessment of the cerebral function.

Methods: The neurological outcome was assessed at 12- to 18-month of age by using the Bayley Scales of Infant Development II. Valuation of the classification of aEEG background pattern, epileptic electrical activity and sleep-weak cycle (SWC) was conducted to develop a new scoring system. The correlation between the summarized scores and outcome analyzed, and the predictive test of the score system was calculated.

Results: A total of 81 infants (39 with asphyxia, 10 with hypoglycemia, 15 with acute bacterial meningoencephalitis, 10 with hyperbilirubinemia and 7 with inborn errors of metabolism) enrolled in the study. The neurological outcome was positive correlated with the background pattern, electrical activity, SWC and summarized scores of the score system based on aEEG. The scoring system has a higher r value, specificity, PPV and lower sensitivity compared with the separate entities such as background pattern, seizures and SWC. The area under the receiver operator characteristics (ROC) curve for predicting outcome by the scoring system was 0.93 (95% CI, 0.878-0.990), with the cut-off value of 7.5.

Conclusions: aEEG maybe a potential tool for monitoring cerebral function in term infants at risk for poor neurodevelopmental outcomes. Our proposed scoring system based on aEEG could quantify information provided by aEEG objectively and could be a good predictor for neurological outcome.

Keywords: Amplitude integrated electroencephalogram (aEEG); full-term infant; neurological disorders

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Introduction

Amplitude integrated electroencephalogram (aEEG) is derived from the original EEG signal by processing to digitally amplify, smooth, rectify, and compress allows for the evaluation of brain function in real time and in over long periods (1), which is considered a method that cannot interfere with routine medical care and the output can be interpreted by nonexperts. In the past four decades, aEEG has been refined and is now widely used in the neonate intensive care unit. It has been used for predicting the neurodevelopment outcome in infants with encephalopathy after asphyxia; monitoring seizures and effects of anticonvulsants; and as a marker for following the neurological maturation of the brain of premature infants (2-9).

Now the technique also has been explored in monitoring

series of critical ill infants by different pathogenesis. Such as severe hypoglycemia can cause aEEG background depressing and seizures showed in an experimental setting (10), but mild hypoglycemia does not change the signal of aEEG significantly (11). And such as moderate unconjugated hyperbilirubinemia cause a transient but delayed suppression of aEEG in preterm infants (12). Furthermore, aEEG could also be used predicted the outcomes of the patients with encephalopathy due to bacterial meningitis (13) and display an upward shift of the lower aEEG amplitude margin or high-frequency burst-suppression (BS) pattern in patients with inborn errors of metabolism (14).

Although there is growing support for the use of aEEG in NICU, the utility for the common neonatal encephalopathy other than HIE has not been well-studied. The comprehensive interpretation of aEEG is limited by challenges in reliably quantifying and summarizing data of encephalopathy caused by different pathogenesis, and the relationship between outcomes and early aEEG monitoring has yet to be determined. Accordingly, our study aims to investigate the relationship between the early aEEG changes of the full term newborn at risk of neurological compromise, and to propose a clinically applicable an aEEG scoring system that will be able to predict an adverse neurodevelopmental outcome early and quantitatively.

Materials and methods

Patients and entry criteria

A total of 81 term newborns at high neurological risk that were treated in a level-III NICU of the Children's Hospital of Zhejiang University School of Medicine between February 2008 and April 2012 were enrolled in the present study. The study was approved by the local ethics committee and the parents of all patients enrolled gave informed consent.

The criteria for the diagnosis hypoxia and ischemia encephalopathy (HIE) (15) includes signs of intrauterine asphyxia, as indicated by late decelerations on fetal monitoring or by meconium staining of the amniotic fluid; evidence of metabolic acidosis (pH less than 7.00, base deficit greater than or equal to 12 mmol/L); early onset encephalopathy; and multi system organ dysfunction. HIE was graded according to Sarnat and Sarnat (16). The criteria of hypoglycemic brain damage was according by Burns *et al*. (17) and Mao *et al*. (18) including: (I) one documented episode of hypoglycemia (blood or plasma glucose concentration of 2.6 mmol/L) associated with acute neurologic dysfunction during the first postnatal week; (II) symptoms included poor feeding, hypothermia, jitteriness, hypotonia, irritability, lethargy, seizures, cyanosis, and apnea; (III) obvious brain injury changes under magnetic resonance imaging (MRI). Acute bacterial meningitis was diagnosed according to the criteria described in avery's diseases of newborn (19), the gold standard for diagnosis of meningitis is the analysis of the cerebrospinal fluid. Acute bilirubin encephalopathy was diagnosed according to Johnson *et al*. (20): with unconjugated hyperbilirubinemia, irritability, and muscular hypertonia accompanied with opisthotonos, and at least one of the following three symptoms, namely lethargy, decreased feeding, hypotonia or hypertonia, high-pitched cry, or abnormal brainstem auditory evoked potential. Inborn error metabolism disease was diagnosed according to corresponding symptoms, along with hyperlactacidemia or hyperammonemia, and determined by tandem mass spectrometry and gas chromatography-mass spectrometry, genetic testing was performed for further confirmation.

Congenital infections, major malformations, multiple dysmorphic features and/or chromosomal abnormalities were excluded.

aEEG and analysis

The aEEG recording (NicoletoneTM Monitor) was applied by the attending neonatologist. Skin was cleaned with a dermabrasive cream and covered with collodium before disc electrodes were placed and fixed in their positions at FP1, FP2, C3, C4, and reference Fz, using the international ten-twenty system of electrode placement. The upper limit of tolerated impedance was 5 kΩ. Frequencies lower than 2 Hz or higher than 20 Hz were filtered. The aEEG signal was displayed on a semi-logarithmic scale at a speed of 6 cm/h (21). The aEEG tracings were reviewed by two clinicians who were blinded to the clinical data. The following channel pairs were used in the present study: FP1-FP2, FP1-C3, FP2-C4, and C3-C4 for aEEG, C3-C4 for burst density and inter-burst interval (IBI). Monitoring was installed as soon as possible and continued until patients were stable or died.

Classification of aEEG background pattern

According to the criteria described by Hellström-Westas *et al*. (22): (I) continuous normal voltage (CNV): continuous activity with lower (minimum) amplitude around >5 μV and maximum amplitude >10 μV; (II) discontinuous voltage (DC): discontinuous background with minimum amplitude

Table 1 Scoring system based on aEEG for term infants at risk for neurological sequelae

Score	aEEG background pattern	Epileptic electrical activity	SWC
1	CNV	No sign	Developed
			immature
2	NC	Single seizure	No
3	BS+	Repetitive seizures	
4	BS–	Status epilepticus	
5	CLV		
6	FT		

CNV, continuous normal voltage; DC, discontinuous voltage; BS, burst-suppression; CLV, continuous low voltage; FT, flat; SWC, sleep-wake cycling.

variable, but mainly below 5 μV, and maximum amplitude over 10 μV; (III) BS: discontinuous background with minimum amplitude without variability at 0-1 [2] μV, and bursts with amplitude >25 μV. BS+ means burst density ≥100 bursts/h, and BS– means burst density <100 bursts/h; (IV) continuous low voltage (CLV): continuous background pattern of very low voltage (around or below 5 μV); and (V) inactive, flat (FT): mainly inactive (isoelectric tracing) background below 3-5 μV.

Classification of sleep-wake cycling (SWC) (22)

SWC in the aEEG is characterized by smooth sinusoidal variations, mainly in the minimum amplitude. The broader bandwidth represents discontinuous background activity during quiet sleep (trace alternant EEG in term infants), and the narrower bandwidth corresponds to more continuous activity during wakefulness and active sleep. (I) No SWC: no cyclic variation of the aEEG background; (II) imminent/immature SWC: some, but not fully developed, cyclic variation of the lower amplitude, but not developed as compared to normative gestational age representative data; (III) developed SWC: clearly identifiable sinusoidal variations between discontinuous and more continuous background activity with cycle duration 20 min.

Seizures (6)

Epileptic seizure activity in the aEEG is usually seen as an abrupt rise in the minimum amplitude, usually accompanied by a simultaneous rise in the maximum amplitude and often followed by a short period of decreased amplitude. The classification of epileptic seizures was as follows: (I) single seizure; (II) repetitive seizures (≥3 seizure patterns during a 30-minute period); and (III) status epilepticus (SE) continuous seizure pattern for ≥30 minutes, presenting as a "saw tooth pattern" or as continuous increases of the lower and upper margins.

Scoring system based on aEEG for term infants at risk for neurological sequelae

The aEEG tracing provided data on the aEEG background pattern, epileptic electrical activity and SWC and was scored as shown in *Table 1*. The three variables were combined create a cerebral function monitoring scores which was calculated by summarizing the scores of the three column. The cerebral function monitoring scores were classified three grades as ≤4, >4-≤8, and >8.

Follow-up study

Follow-up study was performed by a physiotherapist or neurologist who was blinded to clinical course. Neurodevelopmental outcomes were assessed by using Bayley Scales of Infant Development, Second Edition (23) when the infants were 12 to 18 months of age. Cerebral palsy was defined as a psychomotor development index (PDI) <70 and, mental deficiency was defined as a mental development index (MDI) <70 and confirmed by Bayley intelligence text. Outcomes were classified into four groups: without deficit (normal); cerebral palsy and/or mental deficiency or with motor or mental retardation (abnormal); death prior to discharge; infants were lost to follow up.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 software package. Spearman's rank correlation analysis and Chi-square test were performed to investigate the correlation between aEEG tracing and neurodevelopment outcome, $P<0.05$ was considered as statistically significant. Sensitivity, specificity, positive and negative predictive values were calculated in order to evaluate the aEEG' predictivity for neurological evolution. The area under the receiver operator characteristics (ROC) curve was calculated to evaluate the value of scoring system based on aEEG in predicting neurological outcome in term infants. Youden's index was calculated to determine the cut-off value and area under curve (AUC) >0.9 was considered to confer high diagnostic value.

Results

A total of 81 critical ill infants completed aEEG tracings, the mean gestational age was 38.2 (36-42^{+3}) wks, and mean birth weight was 3,202 g (1,800-4,500 g). Monitoring started at 10 [2-20] hours of life, or after admitted in NICU. The mean correct age was 39.5 (36-42^{+5}) when started to monitoring and the mean duration of monitoring was 47.8 [15-96] hours. Twenty-five of the infants died and 48 infants required ventilation during the study period. A total of 39 infants were diagnosed with moderate or severe HIE. Ten infants were diagnosed with hypoglycemic brain damage. A total of 15 infants were diagnosed with acute bacterial meningoencephalitis. Ten infants were diagnosed with acute bilirubin encephalopathy. Five infants were confirmed to have ornithine transcarbamylase deficiency (OTCD), and two infants with methylmalonic academia.

The examples of the representative tracing analysis were shown in *Figures 1-4*. The aEEG features of the total

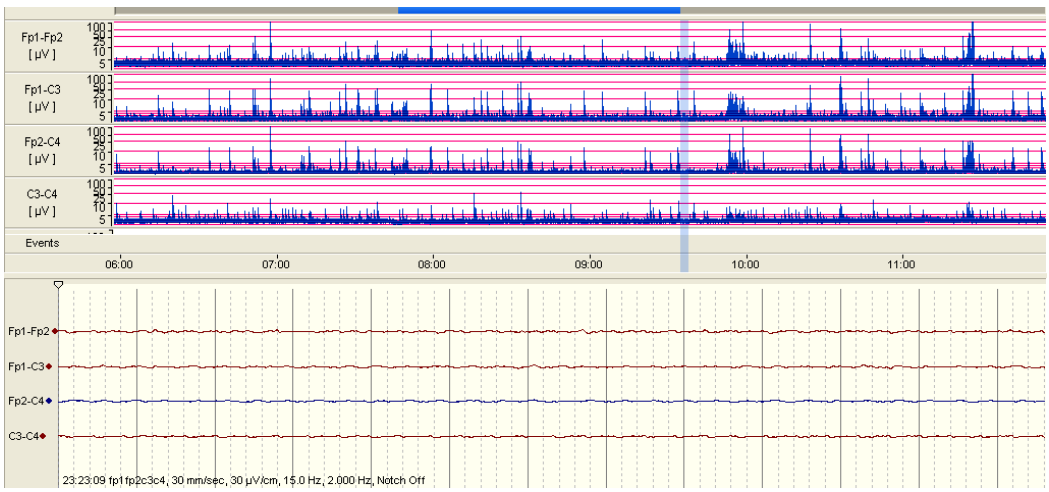

Figure 1 The full-term infant with severe HIE had a mainly inactive, i.e., flat tracing background pattern. The infant died in neonatal period. HIE, hypoxia and ischemia encephalopathy.

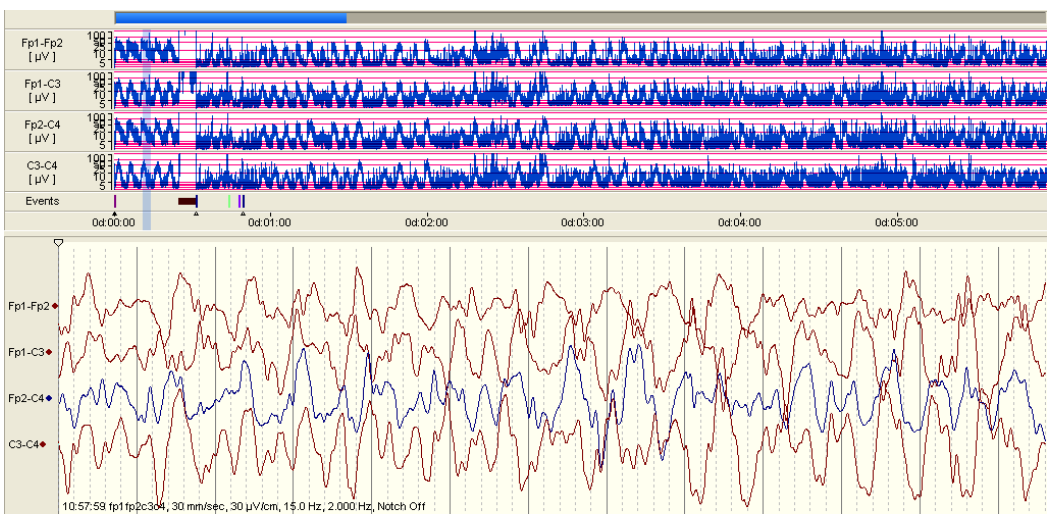

Figure 2 The infant was diagnosed hypoglycemia bran damage born at 36 weeks' gestation and birth weight was 1,800 g, he was found cyanosis and seizures and was taken to the local hospital, where the first blood glucose was 0.4 mmol/L. He was deteriorated quickly and needed resuscitation and transferred to NICU. The aEEG showed electrographic status epilepticus, and abnormal burst-suppression negative background pattern were displayed in the following aEEG monitoring. The lower part of the figure displayed epileptic electrical activity at 12 s in raw EEG. This infant could not wean from ventilator and died in neonatal period. aEEG, amplitude integrated electroencephalogram.

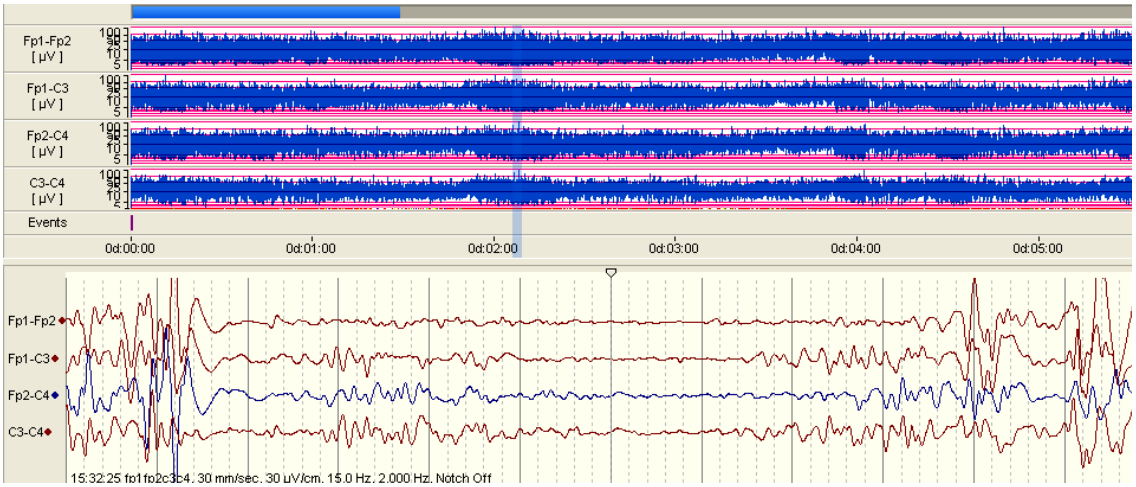

Figure 3 Another infant with hypoglycemic brain injury had continuous normal voltage background pattern with cycling. The lower part of the figure displayed alternative background rhythm in static sleep stage in raw EEG. The infant outcome is good.

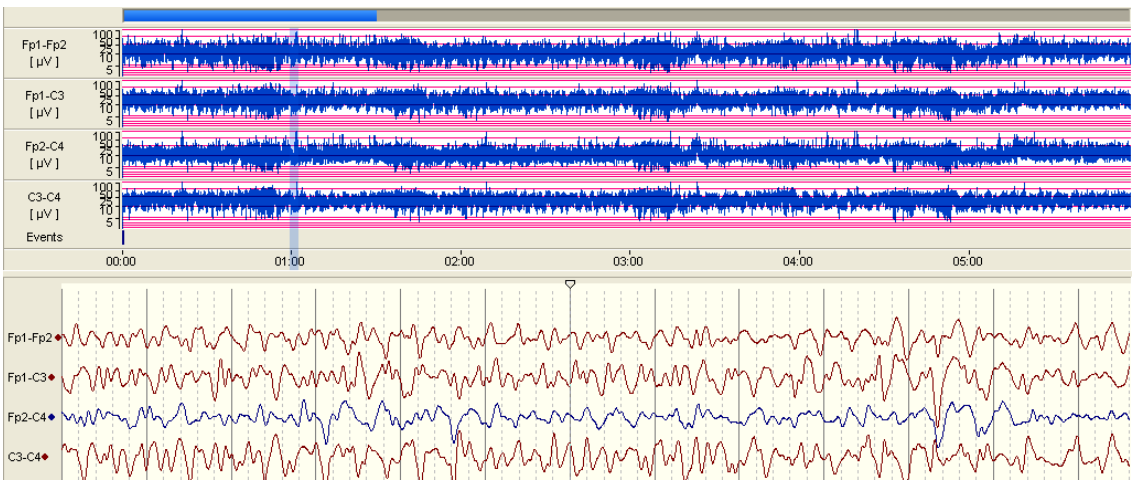

Figure 4 The infant with acute bilirubin encephalopathy. aEEG displayed a continuous normal voltage background pattern with cycling but also with status epilepticus. The lower part of the figure displayed epileptic electrical activity in regular electroencephalogram (the time corresponding with gray line in aEEG tracing). The infant outcome is abnormal. *Figures 1-4* displayed the 6-hour tendency charts of cerebral function monitoring in four infants (the upper part of the figures) and changes in raw electroencephalogram at corresponding time points (the lower part of the figures). aEEG, amplitude integrated electroencephalogram.

infants (including background pattern, SWC and epileptic electrical activity) and neurodevelopmental outcomes for the 81 infants at 12- to 18-month are displayed in *Tables 2* and *3*.

The relationship between the follow-up study and the aEEG tracing changes (*Table 4*) revealed that the infants' aEEG background pattern were FT, CLV, or BS– who often had poor outcome (died or abnormal): 10 infants with FT lasting for more than 24 hours all died; 4 of the 11 with CLV and 7 of the 11 with BS– also died, and the remaining 7 infants with CLV, 3 infants with BS– had delayed psychomotor development, just 1 infant with BS– was healthy. The aEEG background pattern was CNV in 20 infants, all these infants survived: 15 were healthy, 5 had delayed psychomotor development (*Table 4*).

In another hand, the aEEG features of the infants that died in neonatal period showed as follows: ten infants with FT, two infants with CLV/SE (status epileptics in addition to CLV), two infants with CLV/repetitive seizures, six infants with BS–/SE, one infant with BS–/repetitive

Table 2 aEEG findings of the 81 high risk infants

Primary disease [n]	aEEG background pattern [n]						SWC [n]			Epileptic electrical activity [n]			
	CNV	DC	BS+	BS–	CLV	FT	Developed	Immature	None	None	Single seizure	Repetitive seizures	SE
HIE [39]	5	3	10	5	11	5	3	2	34	14	6	5	14
Hypoglycemic brain injury [10]	4	4	1	1	0	0	2	3	5	2	1	2	5
Meningoencephalitis [15]	6	1	3	2	0	3	0	8	7	6	2	3	4
Bilirubin encephalopathy [10]	5	4	1	0	0	0	2	5	3	2	2	2	4
OTCD [5]	0	0	1	2	0	2	0	0	5	0	0	0	5
Methylmalonic academia [2]	0	0	1	1	0	0	0	0	2	1	0	0	1
Total [81]	20	12	17	11	11	10	7	18	56	25	11	12	33

aEEG background pattern were categorized CNV (n=20), DC (n=12), BS+ (n=17), BS– (n=11), CLV (n=11), and FT (n=10); 7 with developed SWC, 18 with immature SWC and 56 without SWC; epileptic electrical activity was detected in 56 infants: 11 with single seizure, 12 with repetitive seizures, and 33 with status epilepticus. HIE, hypoxia and ischemia encephalopathy; OTCD, ornithine transcarbamylase deficiency; SWC, sleep-wake cycling; CNV, continuous normal voltage; DC, discontinuous voltage; BS, burst-suppression; CLV, continuous low voltage; FT, flat.

Table 3 The follow up of the 81 high risk infants

Primary disease [n]	Neurodevelopment outcome			
	Death [n]	Lost to follow-up [n]	Abnormal [n]	Normal [n]
HIE [39]	9	1	16	13
Hypoglycemic brain damage [10]	3	1	2	4
Meningoencephaliti [15]	6	1	3	5
Bilirubin encephalopathy [10]	1	1	6	2
OTCD [5]	5	0	0	0
Methylmalonic academia [2]	1	0	1	0
Total [81]	25	4	28	24

HIE, hypoxia and ischemia encephalopathy; OTCD, ornithine transcarbamylase deficiency. In the total of 81 infants, 25 died, 4 lost to follow-up, 28 survived with delayed psychomotor development or neurological handicap, and 24 were normal.

seizures, one infant with BS+/SE, one infant with BS+/ repetitive seizures, two infants with DC/SE. which revealed that pathological aEEG background pattern including in addition to SE or repetitive seizures is a predictor for poor outcome (*Table 4*).

The thirdly the result also showed that 6 of 7 infants who had developed SWC were recovered and had good outcome while 58 infants were found without SWC, only 12 of these infants had good outcome (*Table 4*).

There was a positive correlation between aEEG background pattern, SWC, epileptic electrical activity and neurodevelopment outcome; which was confirmed by spearman correlation test. Similar correlation was also found between the cerebral function monitoring total scores and neurological outcome, and the scoring system has a higher r value than other separated entities (*Table 4*). Predictive test showed the cerebral function monitoring total scores also has a higher specificity, PPV, but lower sensitivity compared with the separate entities such as background pattern, seizures and SWC (*Table 5*). The area under the ROC curve was calculated to evaluate the value of scoring system based on aEEG in predicting neurological outcome, and the AUC was 0.934 (P<0.001) (95% confidence interval, 0.878-0.990). Youden's index was calculated, and the value of 7.5 was chosen as the cut-off value that could provide a high sensitivity and specificity simultaneously (*Figure 5*).

Discussion

In the present study, we analyzed the data of aEEG in the acute stage of 81 infants with high neurological risks which was not limited to brain damage after asphyxia. The other diagnoses included hypoglycemia brain injury, acute bacterial meningoencephalitis, acute bilirubin encephalopathy, and inborn errors of metabolism. Our results showed that the abnormal aEEG changings of severe

Table 4 Relationship between aEEG features and outcome in term infants with high neurologic risk

	Outcome		
	Normal (n)	Abnormal (n)	Died (n)
aEEG background pattern			
CNV	15	5	0
DC	2	6	2
BS+	6	7	2
BS–	1	3	7
CLV	0	7	4
FT	0	0	10
SWC			
Development	6	1	0
Immature	6	6	0
None	12	21	25
Epileptic electrical activity			
None	16	1	8
Single	5	6	0
Repetitive	2	6	4
SE	1	15	13
Cerebral function monitoring scores			
≤4	10	0	0
>4-≤8	13	11	0
>8	1	17	25

Relationship between aEEG background pattern and prognosis (χ^2=56.243, P<0.001; r=0.694, P<0.001); relationship between SWC and prognosis (χ^2=19.873, P<0.001; r=0.473, P<0.001); relationship between epileptic electrical activity and prognosis (χ^2=47.429, P<0.001; r=0.732, P<0.001); relationship between score of brain function and prognosis (χ^2=54.865, P<0.001 r=0.787, P<0.001); aEEG, amplitude integrated electroencephalogram; SWC, sleep-wake cycling.

Table 5 The predictive value of aEEG features and abnormal prognosis in term infants with high neurologic risk

Predictor	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
aEEG background pattern	90.57	57.69	84.20	75.00
SWC	86.79	50.00	79.31	63.16
Epileptic electrical activity*	83.72	83.72	92.31	75.00
Cerebral function monitoring scores	79.25	95.83	97.67	67.65

PPV, positive predictive value; NPV, negative predictive value; aEEG, amplitude integrated electroencephalogram. Abnormal and died outcomes were put together as one outcome group. Sensitivity, true positive/(true positive + false negative); specificity, true negative/(true negative + false positive); positive predictive value, true positive/(true positive + false positive); negative predictive value, true negative/(true negative + false negative). *, the predictive test of the epileptic activity was analyzed after the 10 cases of FT background pattern were excluded.

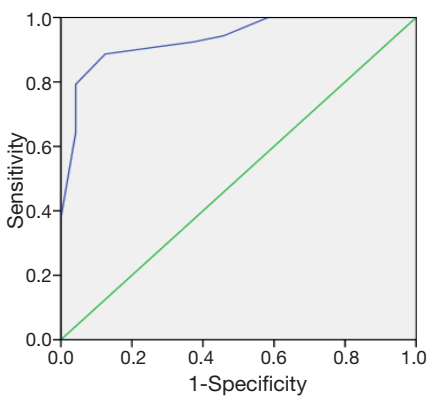

Figure 5 Receiver operator characteristics (ROC) curve of using scoring system based on aEEG to predict the neurological prognosis of infants with high nervous system risks in NICU. AUC; 0.934 (P<0.001) (95% CI, 0.878-0.990); Youden's index: 7.5.

neurological disorders of term infants are similar to that of infant' with severe HIE.

The characteristics of EEG and aEEG vary greatly for infants with different gestational age. Burdjalov and colleagues (24) developed a scoring system which consists of Co (continuity of the recording), Cy (presence of SWC), LB (lower border amplitude score), and B (bandwidth), to assess objectively the developmental maturation of the neurologically unpaired premature. However, for full-term infants or infants with same gestational ages of those brain-injured neonates, there is still no a valuable tool to quantify changes of aEEG, the evaluation cerebral function by aEEG is mainly based on single parameter in previous researches. Such as Toet Mc and Hellström-Westas group showed the aEEG background pattern early within 6-h after birth could predict the severity of HIE (3), Osredkar *et al*. showed that sleep wake cycling was a predictor of good outcome when appearing within 36 hours, and associated with higher scores on Griffith Developmental Quotient (25).

Three parameters including aEEG background, electro physiologic maturity and electrographic seizures should be all evaluated in the interpretation of aEEG described by El-Dib *et al*. (26). Amplitude suppression (voltage suppression) was considered to be the result of brain damage (27), discontinuous EEG signal with a broader aEEG bandwidth and the BS pattern (a flat lower margin interrupted by brief spikes of higher amplitude activity) were also suggesting of encephalopathy (22). Shany *et al*. speculated the background pattern is more sensitive than voltage measurements when evaluating the cerebral function (28). We chose the background pattern as the first component of the scoring system in the study. Furthermore, electrophysiological maturity is intimately connected to the development of SWC. The emergence of cycling depends on the level of integration of cerebral function (25). So the cycling is another important parameter for evaluating the cerebral function. The thirdly is presence or classification of electrographic seizures, seizures would likely to increase neuronal injury, and have an adverse effect on the neurodevelopmental outcome, especially recurrent seizures and SE (29-31). Accordingly we developed the new scoring system incorporates the above three individual component variables of the aEEG features to evaluate objectively and comprehensively the cerebral function of full-term infants who were at increased risk of abnormal neurological events or adverse neurodevelopment outcomes.

The results from correlation study revealed the cerebral function monitoring scores we proposed in this paper has a higher r value then the three individual items. The score system is feasible for clinical using by neonatologist; the lower score stands for better neurodevelopmental outcome and the higher score for bad ones. And we also found that the infant with the score higher than 8 (the cut-off value the ROC curve was 7.5) was with poor outcome. So this scoring system may be more useful than single parameter such as background pattern or electrical activity or SWC because it can afford comprehensive and quantifying data.

The limitation of the score system may decrease the sensitivity (79.25%) of prediction because the compound sum score added from serial inter-relative items. So cerebral function monitoring scores system has a higher specificity, PPV but lower sensitivity compared with the separate entities such as background, seizures and SWC. It can be thought of that separate entities of aEEG and the total CFM score have their respective advantages and disadvantages, and also have certain guiding clinically.

Conclusions

Our findings suggested that using aEEG could provide useful information of cerebral function of infants with high nervous system risks in NICU, and the new scoring system we proposed for term infants may be as a semi-quantitative tool evaluating neonates following high risk events regardless of their cause, it could help guide the extent of the clinical work and refine long-term follow up of these patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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