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Original Article

Early Amplitude-Integrated Electroencephalography Predicts Long-Term Outcomes in Term and Near-Term Newborns With Severe Hyperbilirubinemia

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ABSTRACT

Background: We aimed to determine the predictive neurological prognostic value of early amplitude-integrated electroencephalography (aEEG) in term and near-term neonates with severe hyperbilirubinemia compared with cranial magnetic resonance imaging (MRI) and auditory brainstem response (ABR).

Methods: Infants of ≥35 weeks of gestation with severe hyperbilirubinemia (total serum bilirubin [TSB] ≥340 μmol/L) or with hyperbilirubinemia (TSB ≥257 μmol/L) in association with bilirubin-induced neurological dysfunction were recruited. All the subjects had an aEEG after being admitted to the neonatal intensive care unit, whereas cranial MRI and ABR were performed when TSB had come down to the normal range. All the infants were followed up to 12 months.

Results: During the study period, 77 of 83 infants were eligible, of which 71 had severe hyperbilirubinemia and six had hyperbilirubinemia in association with bilirubin-induced neurological dysfunction. Thirty-three infants were diagnosed with acute bilirubin encephalopathy (ABE), two of whom died of ABE, and 62 completed the follow-up, of which 12 infants had adverse outcomes. Sixty-four infants underwent aEEG, 40 infants had cranial MRI, and 39 infants had ABR. Logistic regression and the receiver-operator characteristic curve analysis showed that the ability of severely abnormal aEEG to predict adverse neurological outcomes in severe hyperbilirubinemia was no better than abnormal ABR, with a sensitivity of 35.7% versus 83.3%, a specificity of 92.0% versus 74.1%, a positive predictive value of 55.6% versus 58.8%, and a negative predictive value of 83.6% versus 90.9%.

Conclusions: Early aEEG could predict adverse neurodevelopmental outcomes in neonates with severe hyperbilirubinemia, although the sensitivity was lower than ABR.

Introduction

Neonatal hyperbilirubinemia is ubiquitous in the first days of life in human infants.[1,2] Under certain conditions it can result in acute bilirubin encephalopathy (ABE), which has significant mortality of up to 21.4%,[3] or in long-term neurodevelopmental disabilities,[4,5] including cerebral palsy (CP),[6,7] auditory disorders,[8,9] and general developmental delays.[10] However, prompt and effective monitoring and interventions (a so-called crash-cart approach)[11] might reverse bilirubin neurotoxicity during the early phases of ABE.[12] Thus to prevent subsequent kernicterus spectrum disorders, it is essential to identify an appropriate monitoring strategy for recognizing ABE.

Conflict of interest: The authors have declared that no conflict of interest exists.

Author contributions: C.Z. and J.S. designed the research; X.Y., L.G., Y.C., H.D., R. Z., S.L., X.D., Y.W., and F.X. performed the data collection; C.Z., Y.X., J.S., Y.C., and L.G. analyzed the data; and Y.X., J.S., and C.Z. wrote the manuscript.

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Cranial magnetic resonance imaging (MRI)[13,14] and auditory brainstem response (ABR)[15,16] are currently available methods that can be used to identify ABE; however, whether amplitude-integrated electroencephalography (aEEG), which is a relatively young and burgeoning method of brain function monitoring, also predicts ABE remains unclear.

Bilirubin damages both neurons and astrocytes[3,17] and typically affects the basal ganglia and subthalamus,[3,18,19] which are closely correlated with the electrical activity of cortical neurons.[20-22] Previous research using conventional electroencephalography (EEG) has identified diverse abnormal courses of EEG patterns under varying degrees of hyperbilirubinemia in term neonates.[23,24] For example, video EEG in newborns with jaundice clearly predicts the onset of seizures in the temporal and occipital lobes of newborns with total serum bilirubin (TSB) levels greater than 340 μmol/L (17.1 μmol/L = 1 mg/dL of bilirubin; thus 340 μmol/L = 19.9 mg/dL).[22] However, studies on the predictive role of aEEG in jaundice patients have yielded conflicting results.[25,26] Here, we report the potential contribution of aEEG to the prediction of prognosis of ABE.

Subjects and methods

Subjects

Subjects included term and near-term infants of ≥35 weeks of gestation in our neonatal intensive care unit (NICU) with severe hyperbilirubinemia (TSB levels ≥340 μmol/L) or with hyperbilirubinemia (TSB levels ≥257 μmol/L) TSB 340 μmol/L = 19.9 mg/dL and TSB 257 μmol/L = 15 mg/dL) in association with the presence of bilirubin-induced neurological dysfunction (BIND).[27] Infants with brain injury with explicit causes (e.g., type III-IV intracranial hemorrhage, moderate to severe hypoxic-ischemic encephalopathy, hypoglycemic brain injury, purulent meningitis, and congenital brain abnormality), chromosomal disease, or hereditary metabolic diseases were excluded according to the study design. All relevant clinical data such as birth weight, gestational age at birth, sex, mode of delivery, age at admission, TSB levels, C-reactive protein, and potential causes of hyperbilirubinemia were collected. ABE is defined as a clinical syndrome including one or more tone abnormalities (such as hypotonia alternating with progressive hypertonia of the extensor muscles along with retrocollis and opisthotonos), varying degrees of irritability or lethargy, decreased feeding and irritability, and shrill or inconsolable crying.[28] The BIND score, which indicates the grade of ABE (subtle ABE score of 1 to 3, moderate ABE score of 4 to 6, and advanced ABE score of 7 to 9), was documented according to the Johnson et al.[29] The treatment protocol includes exchange transfusion and phototherapy according to the criteria of the American Academy of Pediatrics.[30] All infants received phototherapy as soon as they were admitted to the NICU, and exchange transfusion was performed with the permission of the parents. Infants in this study underwent aEEG and MRI or ABR or both MRI and ABR in the hospital and were followed up to 12 months for neurodevelopmental outcomes. All the patients were from the NICU of the Third Affiliated Hospital of Zhengzhou University, which is the headquarters of the Henan provincial severe neonatal transfer network that covers about 109 million inhabitants. The ethics committee of the Third Affiliated Hospital of Zhengzhou University approved this study.

Amplitude-integrated electroencephalography

The aEEG trace was recorded for at least four hours with a NicoletOne device (Nicolet Biomedical Inc, Madison, WI, USA) within 6 to 48 hours of the infant being admitted to the NICU with peak TSB levels before exchange transfusion. The aEEG recordings were assessed using a combination of criteria for amplitude, background activity, and sleep-wake cycling (SWC)[1]: normal—continuous normal amplitude (upper margin >10 μV and lower margin >5 μV), SWC matched to corresponding age, and no electrographic seizures[2]; mildly abnormal—discontinuous activity and mildly abnormal amplitude (upper margin >10 μV and lower margin <5 μV) with immature and delayed SWC or normal amplitude with electrographic seizures; or[3] severely abnormal—discontinuous activity and severely abnormal amplitude (upper margin <10 μV and lower margin <5 μV) without SWC, including burst-suppression (discontinuous activity with lower margin at a constant 0 to 1 μV and a burst amplitude >25 μV), flat trace (electrical silence), continuous low voltage (continuous very low amplitude activity at about 5 μV or <5 μV), or mildly abnormal amplitude with electrographic seizures.[31]

Cranial magnetic resonance imaging

Cranial MRI was performed using a 1.5 T MRI scanner (General Electric Company) within 24 hours of the time the TSB had come down to a normal range (TSB <257 μmol/L). Symmetric hyperintense signal in the globus pallidus on MRI-T1W1, assessed by referring to the putamen T1WI signal of the same child and the difference between the globus pallidus and the putamen T1WI signal of normal newborns of the same postnatal age, was considered an abnormal MRI.[13,14]

Auditory brainstem response

Within 24 hours of the TSB becoming <257 μmol/L, the ABR test was performed in both ears with a Biological Navigator Evoked Response System (Smart-EP, Miami, FL, USA) using 80 decibel (dB) normal hearing level broadband stimuli under reverse polarity (condensation and rarefaction) and at a repetition rate of 19.1/second with the subjects lying supine in the crib and a skin temperature >35.5°C. Infants with absent or abnormal (prolonged interwave intervals or diminished amplitudes or both) wave I, III, and V at 80 dB normal hearing level were diagnosed with abnormal ABR.[8,32]

Follow-up

All the infants were followed up for physical and neurological development every month for six months and then every three months until age 12 months. Bayley Scales of Infant Development, Second Edition, was used to evaluate the intellect and behavior at age 12 months.[33] Infants with psychomotor developmental index less than 70 were referred to rehabilitation physicians for further diagnosis of CP. Adverse outcome was defined as death because of ABE or survival with one or more of CP,[34,35] mental developmental index less than 70, auditory disorder, visual anomaly (paralysis of upward gaze or corrected visual acuity less than 0.05), and/or dental enamel dysplasia.

Data collection

The aEEG, ABR, and MRI results were interpreted independently by two experienced electrophysiologists, otolaryngologists, or radiologists who were not aware of TSB and neurological outcome. Follow-up evaluations were performed by experienced neurologists who were not aware of TSB outcome. The investigators collected and analyzed the clinical and follow-up data.

Statistical analysis

All variables were analyzed using the SPSS 21.0 software. Quantitative data with normal distribution are presented as means ± S.D., and differences between groups were evaluated using an independent samples *t* test. Non-normally distributed variables are presented as medians (quartile range), and pairs of independent groups were compared using the Mann-Whitney *U* test. For categorical variables, the groups were compared using the χ^2 test. Logistic regression analyses were used to assess risk factors for adverse outcome. The receiver-operator characteristic curve was calculated with Medcalc 18.9 and was used to evaluate the ability of different examinations to identify adverse outcomes. The maximum effectiveness of the examinations was evaluated using the Youden Index. All statistical tests were two-sided, and *P* values <0.05 were considered to indicate statistical significance.

Results

Subject characteristics

A total of 83 term and near-term infants were admitted to our NICU during the study period (Fig 1). Six referred neonates were excluded based on the exclusion criteria, thus 77 neonates were eligible, with an average gestational age 39.0 ± 1.3 weeks (range 35.0 to 42.4 weeks) and an average birth weight of 3412.3 ± 431.2 g (range 2350.0 to 4500.0 g) (Table 1). Of the 77 infants, 71 had severe hyperbilirubinemia and six had hyperbilirubinemia in association with the presence of BIND. A total of 33 were diagnosed with ABE (there were 22 infants with subtle signs of ABE, 10 with moderate ABE, and one with advanced ABE), and 64 infants were analyzed for neurological outcome, of which 50 had favorable neurological outcome, two died of ABE, and 12 had adverse outcomes, including one case of sensorineural deafness and 11 cases of CP, of which one had delayed language developmental and four had auditory disorders (Supplementary Table 1). All 64 infants underwent aEEG, 40 infants underwent MRI evaluations, and 39 infants underwent ABR.

Association of aEEG, MRI, and ABR with adverse neurological outcome alone or in combination

Severely abnormal aEEG and abnormal ABR both had a significant association with adverse neurological outcome ($P < 0.05$). Severely abnormal aEEG combined with abnormal ABR or the three examinations combined together were also associated with adverse neurological outcome ($P < 0.05$). Abnormal MRI alone and in combination with severely abnormal aEEG had no association with adverse neurological outcome ($P > 0.05$) (Table 2).

Prediction of adverse neurological outcomes

We used 20 items as shown in Table 1 for the univariate analysis of adverse outcomes. Item with *P* values <0.05 including TSB, the ratio of total serum bilirubin and albumin, BIND score >3, and exchange transfusion were required for inclusion in the logistic regression analysis with different examinations alone or in combination, respectively, to weight these factors. Logistic regression analysis showed that only severe aEEG abnormality (adjusted regression coefficient, 2.08; standard error, 1.01; $P = 0.03$; odds ratio, 8.034; 95% confidence interval, 1.116 to 57.856) and ABR abnormality (adjusted regression coefficient, 2.69; standard error, 1.12; $P = 0.02$; odds ratio, 14.779; 95% confidence interval, 1.632 to 133.820) were significant risk factors of adverse neurological outcomes and thus could be used as predictors of adverse neurological outcome, whereas abnormalities in MRI or in the combination of different examinations were not correlated with adverse neurological outcomes ($P > 0.05$) (Table 3). Receiver-operator characteristic analysis (Fig 2, Table 4) revealed that abnormal ABR predicted adverse neurological outcomes better with a sensitivity of 83.3%, a specificity of 74.1%, a positive predictive value of 58.8%, and a negative predictive value of 90.9% compared with severe aEEG abnormality with a sensitivity of 35.7%, a specificity of 92.0%, a positive predictive value of 55.6%, and a negative predictive value of 83.6%.

Discussion

The aEEG is widely used in infants with hypoxic-ischemic encephalopathy[36,37] and inborn errors of metabolism,[38] for monitoring seizures[39] and predicting brain injury and neurological outcome in preterm infants,[40,41] and for indicating the level of neurological maturation in preterm infants.[42] However, knowledge of aEEG in relation to icteric infants remains limited and mostly concentrated on one single parameter of the aEEG.[26] In the present work, we have incorporated three individual component variables of aEEG, including amplitude, SWC, and electrographic seizures, and we have shown the predictive and prognostic value of abnormal aEEG for neonatal hyperbilirubinemia.

Although aEEG recordings correlate with cerebral cortical activity, the striatum receives projections from a different area of the cerebral cortex and sends connections to specific basal ganglia nuclei, which in turn project back to the same part of the cortex via the thalamus, and this is broadly recognized as the corticobasal ganglia-thalamic loop.[43] Neuronal electrical activity in the loop achieves synchronization and the cortical circuit generates high-frequency components of EEG in information processing as a response to brain function.[20] Bilirubin changes cerebral metabolism, damages the basal ganglia and subthalamus,[3] and destroys

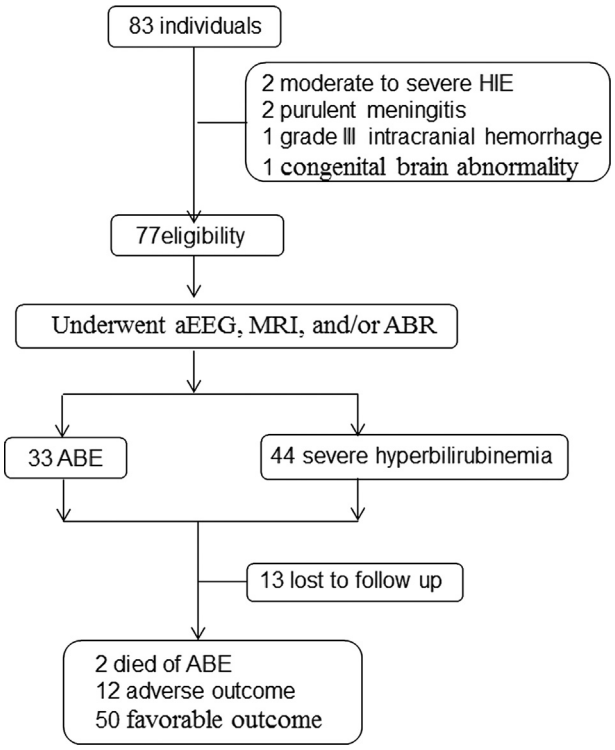

FIGURE 1. Study flow. The schematic flowchart depicting the subjects and neurological follow-up evaluation. ABE, acute bilirubin encephalopathy; ABR, auditory brainstem response; aEEG, amplitude-integrated electroencephalography; HIE, hypoxia ischemia encephalopathy; MRI, magnetic resonance imaging.

TABLE 1.
Study Characteristics

Variables	Eligible Infants (n = 77)	Neurological Outcome (n = 64)		
		Adverse (n = 14)	Favorable (n = 50)	*P* Value
Gestational age (weeks)	39.0 ± 1.3	39.1 ± 1.0	39.1 ± 1.4	0.990
Birth weight (g)	3412 ± 431	3432 ± 297	3412 ± 417	0.868
Male, n (%)	40 (51.9)	8 (57.1)	27 (54)	0.835
Natural-labor/Caesarean delivery	46/31	8/6	32/18	0.639
Age at onset of jaundice (days)	2 (2)*	2 (2)*	2.5 (1.3)*	0.408
TSB at admission (μmol/L)	431 ± 93	493 ± 108	407 ± 83	0.002
ALB at admission (g/L)	36.7 ± 3.1	36.6 ± 2.5	36.8 ± 3.2	0.720
B/A at admission	11.7 ± 2.7	13.5 ± 3.0	11.1 ± 2.2	0.010
BIND score >3, n (%)	13 (17)	6 (43)	6 (12)	0.026
Age at/aEEG (days)	6 (5)*	5.5 (4.5)*	5.0 (9.5)*	0.493
Age at MRI (days)	10.9 ± 4.5	11.0 ± 3.6	10.4 ± 5.0	0.731
Age at ABR (days)	12.6 ± 5.0	11.8 ± 3.4	13.0 ± 6.1	0.540
Hospitalization days	9 (0)*	9 (0)*	8.5 (6.5)*	0.856
Maternal age (years)	28.4 ± 4.5	28.1 ± 5.3	28.4 ± 4.4	0.814
ABO hemolysis, n (%)	19 (24.7)	2 (14.3)	12 (24)	0.681
Rhesus isoimmunization, n (%)	10 (13)	2 (14.3)	3 (6)	0.647
Neonatal infection, n (%)	7 (9.1)	3 (21.4)	4 (8)	0.435
Hemorrhage grade I-II, n (%)	5 (6.5)	0	5 (10)	0.348
Exchange transfusion, n (%)	43 (55.8)	13 (92.9)	21 (42)	0.001
Age at exchange transfusion (days)	6 (4)*	7 (4)*	4 (4.5)*	0.023

Abbreviations:
ABR = auditory brainstem response
aEEG = amplitude-integrated electroencephalography
ALB = serum albumin
B/A = total serum bilirubin/serum albumin
BIND = bilirubin-induced neurological dysfunction
MRI = magnetic resonance imaging
TSB = total serum bilirubin
P value: compared variates between favorable outcomes and adverse outcomes. Quantitative data with normal distribution are presented as means ± S.D.
* Quantitative data with non-normal distribution are presented as medians (quartile range).

the corticobasal ganglia-thalamic loop, leading to various abnormalities in the amplitude, frequency, and continuity of the EEG signal. This finding indicates that aEEG might reflect activity of the deep brain structure, such as the basal ganglia.

Approximately one third of the infants with severe hyperbilirubinemia presented with abnormal aEEG patterns, although most abnormalities were mild, which corroborated previous studies showing that abnormal electrical activity in the cortical

TABLE 2.
Association Between aEEG, MRI, and ABR Individually or in Different Combinations With Adverse Neurodevelopmental Outcomes at 12 Months

Predictor	Adverse Outcome n/Total (%)	Favorable Outcome n/Total (%)	*P* Value
MRI (n = 40)			
Normal	6/11 (54.5)	22/29 (75.9)	0.254
Abnormal	5/11 (45.5)	7/29 (24.1)	
ABR (n = 39)			
Normal	2/12 (16.7)	20/27 (74.1)	0.001
Abnormal	10/12 (83.3)	7/27 (25.9)	
aEEG (n = 64)			
Normal	6/14 (42.9)	37/50 (74)	0.014
Mildly abnormal	3/14 (21.4)	9/50 (18)	
Severely abnormal	5/14 (35.7)	4/50 (8)	
MRI + ABR (n = 22)			
Normal	1/5 (20)	14/17 (82.4)	0.021
Abnormal	4/5 (80)	3/17 (17.6)	
aEEG + MRI (n = 29)			
Normal	6/8 (75)	20/21 (95.2)	0.176
Abnormal	2/8 (25)	1/21 (4.8)	
aEEG + ABR (n = 25)			
Normal	2/6 (33.3)	18/19 (94.7)	0.005
Abnormal	4/6 (66.7)	1/19 (5.3)	
aEEG + MRI + ABR (n = 15)			
Normal	1/3 (33.3)	12/12 (100)	0.029
Abnormal	2/3 (66.7)	0	

Abbreviations:
ABR = auditory brainstem response
aEEG = amplitude-integrated electroencephalography
MRI = magnetic resonance imaging
ABR + MRI, aEEG + ABR, aEEG + MRI, aEEG + ABR + MRI: different combinations of two or three examinations. Abnormal means both or all the examinations were abnormal. Adverse outcome: infants died from ABE or survived with one or more of cerebral palsy, Mental Developmental Index <70, auditory disorder, visual anomaly, and/or enamel dysplasia. n/total: the number of different examination results/the number of different neurological outcomes in the different examinations. *P* value: assessed the association between different examinations with adverse outcomes using χ^2 tests. $P < 0.05$ was considered a significant difference.

TABLE 3.
Logistic Regression Analysis of Different Examinations Individually or in Combination With Adverse Outcome

Predictor	B	SE	*P*	OR	95% CI
Severely abnormal aEEG	2.08	1.01	0.03	8.03	1.12-57.86
Abnormal MRI	0.88	0.99	0.37	2.40	0.35-16.61
Abnormal ABR	2.69	1.12	0.02	14.78	1.63-133.82
MRI + ABR	3.06	1.63	0.06	21.27	0.87-518.36
aEEG + MRI	1.31	1.47	0.37	3.72	0.21-66.64
aEEG + ABR	22.18	—	0.99	—	\
aEEG + MRI + ABR	24.01	—	0.99	—	\

Abbreviations:
ABR = auditory brainstem response
aEEG = amplitude-integrated electroencephalography
B = adjusted regression coefficient
CI = confidence interval
MRI = cranial magnetic resonance imaging
OR = odds ratio
P = assessed the association between different examinations with adverse outcomes using logistic regression
SE = standard error
ABR + MRI, aEEG + ABR, aEEG + MRI, and aEEG + ABR + MRI are different combinations of abnormal MRI, abnormal ABR, and severely abnormal aEEG. $P < 0.05$ was considered a significant difference.

neurons is not uncommon among newborns with jaundice.[22-26,44] Our results suggest that early severe abnormalities in aEEG recordings are correlated with neurological deficits in newborns with severe jaundice, although its sensitivity was only 35.7%, which was very low compared with abnormal ABR with a sensitivity of 83.3%. One reason for this result might be that ABE might be reversible with rapid and aggressive intervention.[12,14] In our study design, aEEG was performed before the exchange transfusion, whereas ABR was carried after the intervention when the patients had stabilized. Another possible explanation for the difference is that hyperbilirubinemia only affects the cerebrocortical electrical activity for a limited time,[23,25] whereas aEEG mainly reflects cortical signal changes. Last but not least, the auditory system is the most sensitive neural system to bilirubin toxicity[8] and might be damaged in isolation regardless of other common regions of the brainstem,[3] thus leading to earlier subtle changes in ABR recordings as an indicator of bilirubin neurotoxicity. Our study showed that ABR is the best predictor for neurological sequelae of bilirubin toxicity, which is consistent with previous studies.[3,5,16]

As is well known, T1-weighted MRI sequences have a high sensitivity for lipid content. Thus myelin, which is present not only in white matter regions, but also in specific gray matter nuclei, including the globus pallidus and subthalamic nucleus, in term or near-term infants would be visualized as high T1-signal because of its high lipid content. Because our predominant diagnostic marker of ABE is also a high signal in these same regions, the predictive value of early MRI might be hindered by confounding abnormal T1-signal with "normal" T1-signal reflecting myelination.[45] On the other hand, increased T1-signal in the globus pallidus at an acute stage of bilirubin encephalopathy is rare[3] and was just 30% (12 of 40) in our study. Both of these explanations might be why we found no positive result for MRI, but it is encouraging that this negative result indeed serves as a clinical resource useful in urging the establishment of a broader monitoring strategy (e.g., ABR and aEEG) for predicting long-term disability of ABE in infants. Except the aforementioned reason, the actual sample size might also have influenced MRI predictive value. In this study, almost half of the parents refused to do cranial MRI or ABR because of sedation to perform MRI or ABR. Furthermore, there was a high rate of lost follow-up (16.9%) in this study. All these factors contributed to a relatively insufficient actual sample size for MRI and ABR, and even smaller sample sizes for their combinations, which led to an actual power of <80% for predicting adverse outcomes. This finding might explain why the combination of different examinations made the prediction even worse.

A weakness of this study was that the normal healthy term control infants were not recruited at the same time. Our inability to dynamically monitor changes in aEEG in severe hyperbilirubinemia infants is another limitation, and further studies with aEEG recording after exchange transfusion or phototherapy might provide more information for the outcomes. Finally, our relatively large prospective study cohort was not big enough and this might have affected the statistical results.

Conclusions

Our findings suggest that aEEG does have predictive and prognostic power for term and near-term neonates with severe hyperbilirubinemia, although its predictive value was not as good as ABR. At the very least, our study indicates that aEEG might be a promising bedside tool that should be investigated in greater detail in the future.

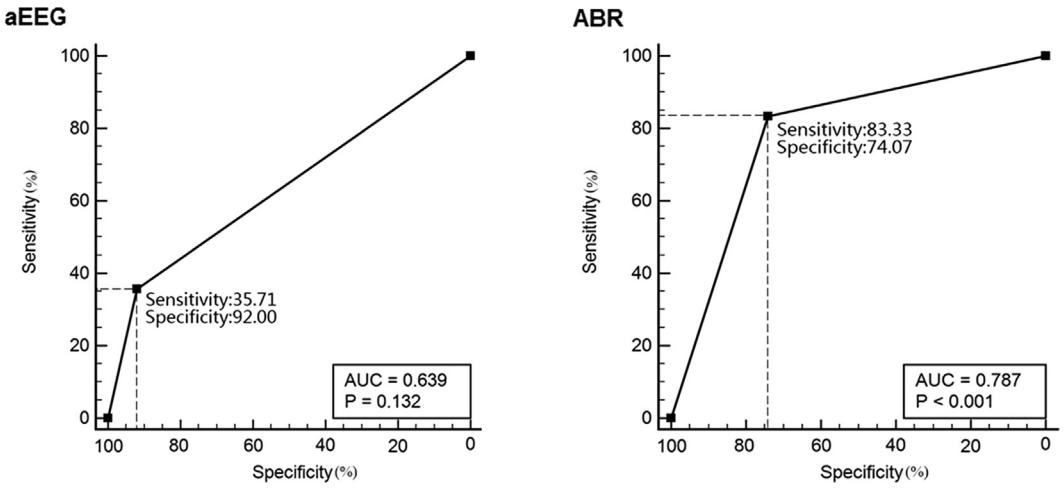

FIGURE 2. Receiver-operator characteristic (ROC) curve of the association between severely abnormal aEEG and abnormal ABR with adverse outcomes. aEEG: The area under the ROC curve (AUC) for severely abnormal aEEG was 0.639. The cutoff value of 0.28 (dashed lines) implies a sensitivity of 35.71% and a specificity of 92.00% for adverse outcomes. ABR: The AUC for abnormal ABR was 0.79. The cutoff value of 0.57 (dashed lines) implies a sensitivity of 83.33% and a specificity of 74.07% for adverse outcomes. ABR, auditory brainstem response; aEEG, amplitude-integrated electroencephalography.

TABLE 4.
Predictive Values of aEEG and ABR

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Severely abnormal aEEG	35.7	92.0	55.6	83.6	79.7
Abnormal ABR	83.3	74.1	58.8	90.9	76.9

Abbreviations:
ABR = auditory brainstem response
aEEG = amplitude-integrated electroencephalography
NPV = negative predictive value
PPV = positive predictive value

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Supplementary data

Supplementary data to this article can be found online at 10.1016/j.pediatrneurol.2019.04.015.

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