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Risk Factor Analysis and Scoring System for Neurodevelopmental Outcomes after Neonatal Seizures

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Abstract

Background: The aims of this study were to determine prognostic factors and to devise a new scoring system for neurodevelopmental outcomes in infants with neonatal seizures.

Methods: A retrospective review of medical records was performed for infants treated for neonatal seizures from March 2010 to December 2015 at the neonatal intensive care unit at Haeundae Paik Hospital. Neurologic outcomes were assessed at the post-conceptional age of 24 months. To assess the risk factors associated with poor neurologic outcomes, various factors including clinical characteristics, EEG findings, and the results from neuroimaging work-ups were analyzed with univariate and multiple logistic regression analyses (SPSS version 18.0).

Results: Of the 174 enrolled infants, 57 (32.8%) showed abnormal neurologic outcomes. Seven potential predictors of adverse outcomes, selected by binary logistic regression analysis, were used to devise a scoring system. These included birth weight, time of onset, EEG findings, neuroimaging results, seizure type and severity and etiology. The variables were assigned binary scores with a total arithmetic composite score ranging from 0 to 7. A cutoff score of ≥ 3 provided the greatest sensitivity and specificity. Normalization or persistent normal findings at follow-up EEG within 3 months after seizure on-set were also associated with neurologic outcomes ($p<0.05$).

Conclusion: We propose scoring system uses seven variables to provide early prognostic information on unfavorable neurodevelopmental outcomes in infants with neonatal seizures and reliably predicts long-term neurologic outcomes at the time of seizure onset.

Keywords: Neonatal seizure; Prognostic factor; Neurodevelopmental outcomes; Scoring system

Introduction

Seizures are one of the most common, and sometimes the only, distinctive clinical manifestations of neurologic dysfunction in newborn infants [1]. Their incidence is significantly higher in the neonatal period than in any other period of life and estimated to occur in 0.3-0.5% of full-term neonates [2]. Seizures can not only indicate acute brain damage, but they may also cause or aggravate brain damage [3].

Despite improvements in neonatal care, the rates of many adverse neurologic sequelae after neonatal seizures remain high [4]. The long-term neurodevelopmental effects of neonatal seizures are still unclear. However, neonatal seizures have been reliably correlated with increased mortality rate and risk for neurologic impairments including cerebral palsy (CP), epilepsy and mental retardation [5,6]. Early intervention all but guarantees a better outcome in neonates with a high risk of neurologic sequelae. The accurate prediction of neurodevelopmental outcomes after neonatal seizures makes it possible to identify such children and provide supportive care including early rehabilitative interventions [7,8].

This retrospective study was conducted to identify prognostic factors that reliably predict neurodevelopmental outcomes in infants with neonatal seizure. Based on our analysis, we developed a scoring system to identify infants at high risk of long-term neurologic sequelae.

Methods

Subjects

We reviewed the medical records of infants admitted to the neonatal intensive care unit (NICU) of the Inje University Haeundae Paik Hospital from March 2010 to December 2015. Infants with clinically evident neonatal seizures (within the first 28 days after birth) were enrolled. The seizures were diagnosed by a neonatologist or pediatrician based on clinical observations using internationally accepted criteria [1]. Infants were enrolled if they had at least 24 months of neurologic follow-up, unless the infant's development was normal in which case 12 months of follow-up was allowed.

Data collected included gestational age, birth weight, gender, mode of delivery, perinatal clinical factor, and Apgar score. Information on electroencephalography (EEG) findings, head ultrasonography (HUS) or brain magnetic resonance imaging (MRI) findings, and clinical course after admission including responsiveness to antiepileptic drugs (AEDs), was also collected. Perinatal clinical factors including the presence of fetal distress, meconium-stained fluid, need for resuscitation in the delivery room and maternal history were also reviewed.

Seizure types were categorized according to Volpe's classification schema, based on the seizure semiology documented in the medical records. The types included subtle, focal clonic, multifocal clonic, myoclonic and tonic. If, multiple types of seizures were recorded, the most prominent was selected.

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This study was approved by the institutional review board of Haeundae Paik Hospital.

Seizure etiology

The etiology of a seizure was determined based on clinical history, neuroimaging studies, and EEG and laboratory test results. We categorized all seizures as having one of the following nine etiologies: (1) perinatal asphyxia including hypoxic-ischemic encephalopathy (HIE), (2) brain hemorrhage, (3) brain infarction, (4) infection including meningitis, (5) temporary metabolic abnormalities, (6) brain developmental anomaly, (7) trauma, (8) rota-virus infection, (9) unknown. Asphyxia was defined as fetal distress and an Apgar score <7 at 5 min. HIE was diagnosed by criteria including metabolic acidosis, evidence of fetal distress, an Apgar score <7 at 5 min and neurologic manifestations within the first 24 h after birth. Metabolic abnormalities included transient hypoglycemia, hypocalcemia and hypocalcemia with hypoglycemia. Chromosome study was performed if a genetic disorder was suspected. When all other possible causes were ruled out, rotavirus infection was assigned in infants with symptomatic rota-viral infection and specific abnormal findings on brain MRI. Because infants with inherited metabolic disorder were transferred to other hospitals for specialized care by a pediatric endocrinologist, this cause of neonatal seizures was excluded from this study.

Treatments

Seizure treatments were classified as follows: Group 1, no treatment was needed as the seizures were controlled shortly after correction of temporary metabolic disturbance or seizures were allowed to self-resolve because they were short and non-repetitive (≤ 2 times); Group 2, seizures were quickly controlled with intra-venous phenobarbital only; Group 3, AEDs other than phenobarbital were needed to control seizures (e.g. levetiracetam and benzodiazepines).

EEG and neuroimaging

If a seizure was diagnosed, inter-ictal EEG monitoring was performed as soon as possible if tolerated (Medelec, Oxford, England). EEG records were reviewed by a pediatric neurologist, and the findings were classified into three groups according to background pattern and epileptic discharges: Group 1, normal or mildly abnormal (i.e., increased sharp activity, absent or decreased frequency of normal patterns, excessively long low-voltage periods, overall slightly decreased voltage); Group 2, moderately abnormal (moderately abnormal asymmetries in voltage or frequencies, increased asynchrony for age, low voltage, epileptic discharge); and Group 3, severely abnormal (burst suppression pattern, severely abnormal isoelectric or low-voltage invariant activity, permanent discontinuous activity). Follow-up EEG was performed at 1 and 3 months after discharge. Additional follow-up EEG was performed in accordance with the decision of a pediatric neurologist. Neuroimaging including HUS or brain MRI was performed in all infants with neonatal seizures. Incidental findings of scanty amounts of subdural hemorrhage or cephalhematoma were classified as negative in this study.

Follow-up and outcomes

Neurodevelopmental outcomes were classified as favorable or adverse by our multidisciplinary team based on the available documentation. Global developmental delay (GDD) was defined as a significant delay in two or more developmental categories, including gross and fine motor, speech and language, cognition, personal-social and activity of daily living. Cerebral palsy, GDD and epilepsy were classified as adverse outcomes.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences software version 18.0 (SPSS Inc., Chicago, IL, USA). The Chi-square and Fisher exact tests were used for categorical variables in group comparisons. The Student t-test and Mann-Whitney U-test were used for double comparisons. To determine risk factors, outcomes were analyzed by multivariate logistic regression analysis. The results were evaluated with a confidence interval of 95%. P-values <0.05 were considered significant.

Receiver operating characteristic (ROC) curves were used to measure the performance of our scoring system in predicting the outcome at 2 years of age. The ROC curve was chosen to show how sensitivity (vertical axis) changed in relation to false-positives (horizontal axis; 1-specificity), because the decision criterion was varied. The area under curve (AUC) is considered a better indicator of predictive accuracy than fixed sensitivity or specificity because it yields an index that is independent of the cut-off point.

Results

During the study period, a total 2,919 infants were admitted, and 196 infants were diagnosed as having neonatal seizure. A total of 10 infants were lost to follow-up and 12 infants died. Ultimately, a total 174 infants were enrolled.

Univariate analysis of clinical characteristics and seizure semiology

The retrospective cohort for analysis comprised 92 (52.9%) males and 82 (47.1%) females. The mean birth weight was 2,752.53 ± 919.25 g (570.0–4940.0 g) and the mean gestational age was 36.0 ± 5 weeks (24.0–41+4 weeks). Birth weight, seizure type, on-set time, response to AED therapy, and presence of status epilepticus were the most significant risk factors for adverse neurologic outcomes in the univariate analysis (Table 1, p<0.05).

Seizure etiology

Table 2 described the etiologies of seizures in full-term and preterm infants. We could not determine the cause of seizures in 34 infants. Chromosome studies were performed in 14 infants. However, there were no specific chromosomal abnormalities that might cause seizures. Asphyxia, brain hemorrhage, and developmental brain anomalies were associated with abnormal neurologic outcomes (Table 1, p<0.05).

EEG and neuroimaging results

EEG was performed within 24 h, 48 h, 72 h and thereafter after seizure on-set in 35, 98, 27 and 29 infants, respectively. Most infants (133/174, 76.4%) were evaluated with EEG within 48 h after seizure. Moderate or severe abnormalities on EEG were found in 36 (20.7%) and 16 (9.2%) infants, respectively. Follow-up EEG was performed for 160 infants. Eventual normalization and/or persistent normal findings on follow-up EEG examinations performed within 3 months after discharge were observed in 117 infants. The remaining 43 infants (43/160, 26.9%) showed persistently abnormal EEG findings which ranged from mild delayed maturation to definite epilepsy.

Brain MRI was performed in 167 infants within 24 h, 48 h, 7 days and thereafter following seizures in 19, 67, 42, and 39 infants, respectively. HUS was performed within 24 h after seizure in all 7 infants. A total of 108 infants (62.1%) showed abnormal neuroimaging findings on HUS and brain MRI (Table 3). Moderate to severe abnormalities of background EEG activities, lack of follow-up EEG normalization within

Variables	Number of infants	Favorable outcome	Unfavorable outcome	p-value
Total		117	57	
Gestational age				
Preterm	49	28 (57.1)	21 (42.9)	0.076
Full term	125	89 (71.2)	36 (28.8)	
Birth weight, g				
ELBW (<1000 g)	17	7 (41.2)	10 (58.8)	<0.001
1,000 g-1,500 g	10	4 (40.0)	6 (60.0)	
1,500 g-2,500 g	16	8 (50.0)	8 (50.0)	
≥ 2,500 g	131	98 (74.8)	33 (25.2)	
Delivery type				
Spontaneous	68	51 (75.0)	17 (25.0)	0.081
Cesarean delivery	106	66 (62.3)	40 (37.7)	
Apgar score at 5 min				
<7	21	8 (38.1)	13 (61.9)	0.002
≥ 7	153	109 (71.2)	44 (28.8)	
Meconium staining				
Yes	28	17 (60.7)	11(39.3)	0.422
No	146	100 (68.5)	46 (31.5)	
Seizure onset, h				
<24 h	66	34 (51.5)	32 (48.5)	0.003
24-72 h	44	26 (70.5)	13 (29.5)	
≥ 72 h	64	60 (81.2)	12 (18.8)	
Seizure type				
Subtle	56	39 (69.6)	17 (30.4)	0.002
Focal clonic	62	33 (53.2)	29 (46.8)	
Multifocal clonic	24	23 (95.8)	1 (4.2)	
Tonic	28	18 (64.3)	10 (35.7)	
Myoclonic	4	4 (100.0)	0 (0.0)	
Treatment				
None+phenobarbital only	145	107 (73.8)	38 (26.2)	<0.001
Additional AED required	28	10 (35.7)	18 (64.3)	
Status epilepticus				
Yes	17	3 (17.6)	114 (72.6)	<0.001
No	157	14 (82.4)	43 (27.4)	
Neuroimaging				
Negative	66	59 (90.8)	7 (10.6)	<0.001
Abnormal	108	58 (53.7)	50 (46.3)	
Proven HIE in Brain MRI				
Yes	58	31 (53.4)	85 (73.9)	0.007
No	115	27 (46.6)	30 (26.1)	
EEG findings				
Normal/mildly abnormal	122	103 (84.4)	19 (15.6)	<0.001
Moderately abnormal	36	13 (36.1)	23 (63.9)	
Severely abnormal	16	1 (6.3)	15 (93.8)	
Follow-up EEG (n=160)				
Normal	117	98 (83.8)	19 (16.2)	<0.001
abnormal	43	10 (23.3)	33 (76.7)	
Etiology of seizure				
Perinatal asphyxia	75	49 (65.3)	26 (34.7)	0.001
Brain hemorrhage	28	12 (42.9)	16 (57.1)	
Vascular infarction	11	8 (72.7)	3 (27.3)	
Sepsis +/- meningitis	10	8 (80.0)	2 (20.0)	
Metabolic disturbance	7	7 (100.0)	0 (0.0)	
Brain anomaly	3	0 (0.0)	3 (100.0)	
Traumatic injury	2	1 (50.0)	1 (50.0)	
Rotavirus infection	4	4 (100.0)	0 (0.0)	
Unknown	34	28 (82.4)	6 (17.6)	

Abbreviations: ELBW: Extremely Low Birth Weight; AED: Anti-Epileptic Drug; HIE: Hypoxic-Ischemic Encephalopathy; MRI: Magnetic Resonance Imaging; EEG: Electroencephalography

Table 1: Bivariate analysis of clinical factors for prediction of neurological outcomes.

	Frequency, n (%)	Preterm infants	Full-term infants
Perinatal asphyxia	75 (43.1)	9 (18.4)	66 (52.8)
Intracranial hemorrhage	28 (16.1)	22 (44.9)	6 (4.8)
Vascular infarction	11 (6.3)	4 (8.2)	7 (5.6)
Sepsis +/- meningitis	10 (5.7)	1 (2.0)	9 (7.2)
Metabolic disturbance	7(4.0)	2 (4.1)	5 (4.0)
Developmental brain anomaly	3 (1.7)	1 (2.0)	2 (1.6)
Trauma	2 (1.1)	0 (0.0)	2 (1.6)
Rotavirus infection	4 (2.3)	0 (0.0)	4 (3.2)
Unknown	34 (19.5)	10 (20.4)	24 (19.2)

Table 2: Etiologies of neonatal seizure.

Variables	Total	Preterm infants N=49	Full term infants N=125	P-value
Birth weight g				
ELBW (<1000 g)	17	17 (100.0)	0 (0.0)	0
1,000 g-1,500 g	10	9 (90.0)	1 (10.0)	
1,500 g-2,500 g	16	11 (68.8)	5 (31.2)	
≥ 2,500 g	131	12 (9.2)	119 (90.8)	
Delivery type				
NSVD	68	13 (26.5)	55 (44.0)	0.034
Cesarean delivery	106	36 (73.5)	70 (56.0)	
Apgar score at 5 min				
1 (<7)	21	7 (14.3)	14 (11.2)	0.574
2 (≥ 7)	153	42 (85.7)	111 (88.8)	
Seizure onset h				
<24 h	66	17 (34.7)	49 (39.2)	0.083
24-72 h	44	18 (36.7)	26 (20.8)	
≥ 72 h	64	14 (28.6)	50 (40.0)	
Seizure type				
Subtle	56	30 (61.2)	26 (20.8)	0
Focal clonic	62	10 (20.4)	52 (41.6)	
Multifocal clonic	24	6 (12.2)	18 (14.4)	
tonic	28	2 (4.1)	26 (20.8)	
myoclonic	4	1 (2.0)	3 (2.4)	
AED				
None + phenobarbital only	145	43 (87.8)	102 (82.3)	0.376
Other AED	28	6 (12.2)	22 (17.7)	
Status epilepticus				
Yes	17	5 (10.2)	12 (9.6)	0.904
No	157	44 (89.8)	113 (90.4)	
Neuroimaging				
Negative	66	11 (22.4)	55 (44.0)	0.008
Abnormal	108	38 (77.6)	70 (56.0)	
Proven HIE in Brain MRI				
Yes	58	8 (16.3)	50 (40.0)	0.003
No	115	41 (83.7)	75 (60.0)	
EEG findings				
Normal/mildly abnormal	122	30 (61.2)	92 (73.6)	0.235
Moderately abnormal	36	14 (28.6)	22 (17.6)	
Severely abnormal	16	5 (10.2)	11 (8.8)	
Follow-up EEG (n=160)				
Normalization or persistent normal findings	117	28 (65.1)	89 (76.1)	0.166
abnormal	43	15 (34.9)	28 (23.9)	
Overall neurologic outcomes				
Favorable	117	28 (57.1)	89 (71.2)	0.076
unfavorable	57	21 (42.9)	36 (28.8)	

Table 3: Abnormal findings of neuroimaging work-ups.

3 months after discharge, and abnormal neuroimaging results were associated with an increased risk of unfavorable neurodevelopmental outcomes (Table 1, $p<0.05$).

Comparison between full-term and preterm neonates

Table 4 shows differences between the full-term and preterm infants. There were no significant differences in clinical findings except for a higher incidence of low birth weight (LBW) in preterm neonates. Subtle seizures were more frequent in preterm neonates, while focal clonic seizures were more frequent in full-term infants. Preterm infants showed higher rates of abnormal neuroimaging findings.

Variables	Total	Preterm infants N=49	Full term infants N=125	P-value
Birth weight, g				
ELBW (<1000 g)	17	17 (100.0)	0 (0.0)	0
1,000 g- 1,500 g	10	9 (90.0)	1 (10.0)	
1,500 g-2,500 g	16	11 (68.8)	5 (31.2)	
≥ 2,500 g	131	12 (9.2)	119 (90.8)	
Delivery type				
NSVD	68	13 (26.5)	55 (44.0)	0.034
Cesarean delivery	106	36 (73.5)	70 (56.0)	
Apgar score at 5 min				
1 (<7)	21	7 (14.3)	14 (11.2)	0.574
2 (≥ 7)	153	42 (85.7)	111 (88.8)	
Seizure onset, h				
<24 h	66	17 (34.7)	49 (39.2)	0.083
24-72 h	44	18 (36.7)	26 (20.8)	
≥ 72 h	64	14 (28.6)	50 (40.0)	
Seizure type				
Subtle	56	30 (61.2)	26 (20.8)	0
Focal clonic	62	10 (20.4)	52 (41.6)	
Multifocal clonic	24	6 (12.2)	18 (14.4)	
tonic	28	2 (4.1)	26 (20.8)	
myoclonic	4	1 (2.0)	3 (2.4)	
AED				
None+phenobarbital only	145	43 (87.8)	102 (82.3)	0.376
Other AED	28	6 (12.2)	22 (17.7)	
Status epilepticus				
Yes	17	5 (10.2)	12 (9.6)	0.904
No	157	44 (89.8)	113 (90.4)	
Neuroimaging				
Negative	66	11 (22.4)	55 (44.0)	0.008
Abnormal	108	38 (77.6)	70 (56.0)	
Proven HIE in Brain MRI				
Yes	58	8 (16.3)	50 (40.0)	0.003
No	115	41 (83.7)	75 (60.0)	
EEG findings				
Normal/mildly abnormal	122	30 (61.2)	92 (73.6)	0.235
Moderately abnormal	36	14 (28.6)	22 (17.6)	
Severely abnormal	16	5 (10.2)	11 (8.8)	
Follow-up EEG (n=160)				
Normalization or persistent normal findings	117	28 (65.1)	89 (76.1)	0.166
Abnormal	43	15 (34.9)	28 (23.9)	
Overall neurologic outcomes				
Favorable	117	28 (57.1)	89 (71.2)	0.076
unfavorable	57	21 (42.9)	36 (28.8)	

Table 4: Comparison of characteristics between full term and preterm infants.

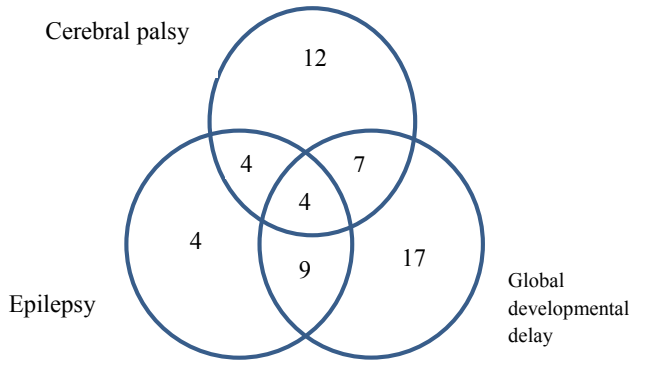

Figure 1: Distribution of neurodevelopmental impairments in the study cohort.

Mortality and neurodevelopmental outcomes

During the study period, 12 enrolled patients died (mortality rate: 6.1%). The leading causes of death were multi-organ failure accompanying bronchopulmonary dysplasia, sepsis and severe asphyxia. Although seizure was not specifically related to death, most of the infants in the mortality group showed a refractory seizure pattern and more severely abnormal findings on neuroimaging and EEG work-ups.

Favorable outcomes were observed in 117 infants (67.2%) and unfavorable outcomes in 57 infants (32.8%). GDD was observed in 37 (21.2%), CP in 27 (15.5%), and epilepsy in 21 infants (12.1%). Figure 1 illustrates the overlapping distribution of the adverse outcomes. The mean follow-up period was 24.17 ± 11.35 months (12–62 months) and 30.12 ± 10.85 months (24–64 months) in each of the favorable and unfavorable outcome groups, respectively. A multiple logistic regression analysis identified LBW, seizure type, EEG background activity, and EEG normalization as independent risk factors for poor neurodevelopmental outcomes (Table 5, $p<0.05$).

Seizure scoring system

Only variables that could be assessed by objective findings and were significant factors in bivariate analysis were selected. Seven potential predictors of adverse outcomes selected by binary logistic regression analysis were included in the scoring system: (1) birth weight, (2) seizure on-set, (3) seizure type, (4) seizure severity; need for additional AEDs other than phenobarbital to control seizure or presence of status epilepticus, (5) EEG findings, (6) neuroimaging results, and (7) seizure etiology. The minimum possible total score was 0 and the maximum was 7. These scores were highly accurate: with an AUC of 0.871 (95% CI: 0.813-0.929, p-value: 0.030) and a cut-off 3, the sensitivity and specificity were 84.2% and 82.1%, respectively (Figure 2). The mean seizure score was significantly higher in infants with adverse outcomes than in those with normal outcomes (3.77 ± 1.69 vs. 1.52 ± 1.15, $p<0.05$). The model accurately predicted outcomes in 82.1% (96/117) of the newborns with favorable outcomes and in 86.0% (49/57) of those with unfavorable outcomes. Overall, the positive predictive value (PPV) was 69.6% and the negative predictive value (NPV) was 91.4%.

Discussion

Previous studies of neonatal seizures reported incidences of long-term sequelae after neonatal seizures ranging from 25% to 45% [9,10]. Thus, despite improvements in perinatal care, the incidence of neurologic sequelae after neonatal seizures remains high. Early detection and appropriate intervention for neonatal seizures are

	Univariate analysis	Multivariate analysis
	OR (95% CI), p-value	**OR (95% CI), p-value**
Gestational age (preterm vs. full-term)	1.517 (0.30 –7.527), 0.610	
Birth weight (LBW vs. Normal)	5.011 (1.104–24.767), 0.048	3.528 (1.269–9.808), 0.016
Delivery type (C/S vs. spontaneous)	1.334 (0.447-3.983), 0.606	
Apgar score at 5 min (<7 vs. ≥ 7)	1.190 (0.244-5.809), 0.830	
Seizure on-set (≥ 24 h vs. <24 h)	0.458 (0.144-1.456), 0.186	
Seizure type (focal clonic vs. others)	2.412 (0.844-6.892), 0.100	2.662 (1.016–6.975), 0.046
Response to AED therapy (phenobarbital only vs. additional AED required)	0.594 (0.068-5.158), 0.637	
Status epilepticus (No vs. yes)	0.383 (0.031-4.790), 0.457	
Neuroimaging (abnormal vs. normal)	2.686 (0.704-10.248), 0.148	
HIE in brain MRI (positive vs. negative)	1.034 (0.707-1.513), 0.862	
EEG background activity (moderate to severe vs. others)	5.962 (1.834-19.385), 0.003	8.248 (3.171–21.457), <0.010
EEG normalization (No vs. yes)	5.996 (1.916-18.762), 0.002	8.114 (2.978–22.103), <0.010
Etiology of seizure (asphyxia, hemorrhage, anomaly vs. others)	1.045 (0.899-1.213), 0.569	

Abbreviations: LBW: Low Birth Weight; C/S: Caesarian Section; AED: Anti-Epileptic Drug; HIE: Hypoxic-Ischemic Encephalopathy; MRI: Magnetic Resonance Imaging; EEG: Electroencephalography

Table 5: Predictors of adverse neurological outcomes of neonatal seizure.

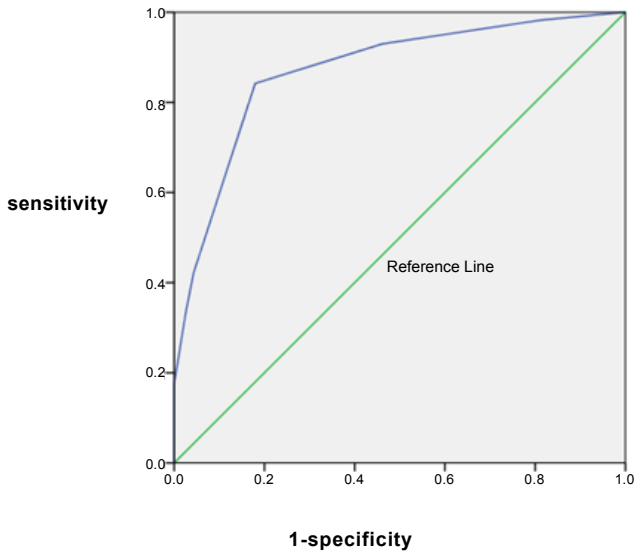

Figure 2: The ROC curve showed that the scoring system is a good indicator of predictive accuracy with an area under the curve of 0.871 (95% CI: 0.813-0.929; p-value: (0.030).

essential for reducing neurologic impairments [3]. Therefore, we made an effort to determine readily discernible risk factors for adverse neurologic outcome after seizures and tried to devise a scoring system for prediction of neurologic outcomes based on clinical and radiologic work-ups that are easily obtained around the time of seizure on-set in typical NICU settings.

Clinical studies have suggested that the underlying etiology of neonatal seizures is one of the main prognostic factors of adverse long-term sequelae [11,12]. Although, multiple etiologic factors for seizures exist in neonates, only a few account for most cases of seizures. HIE, which is reported to occur in 1-2/1,000 live births, is the most prevalent pathology in neonatal seizures. HIE, brain hemorrhage, intracranial infection, and developmental disorders are responsible for 80-90% of all cases of neonatal seizures [1]. HIE and intra-cranial hemorrhages were the leading causes of neonatal seizures in the present study. We were able to diagnose perinatal arterial stroke in 11 infants. In tests conducted to rule out an underlying thrombotic disorder, protein C/S deficiency was diagnosed in one infant. Recently, increasing evidence has suggested that rotavirus infection is associated with neonatal seizures in infants with diffuse cerebral white matter lesions [13-15] and four infants in this study showed similar clinical and radiologic findings. HIE, hemorrhage, CNS infection, and cerebral malformation are known to convey a greater risk for adverse outcomes than other causes of neonatal seizures [16,17], as was the case in our study. Transient metabolic disturbance, rota-viral infection, and idiopathic seizures were associated with favorable outcomes.

Clinical variables including gestational age, birth weight, Apgar score, need for resuscitation at birth and seizure on-set, seizure types, and status epilepticus are also known prognostic factors for neurologic outcomes [18-21]. Consistent with our results, previous studies have shown that full-term infants who experienced seizures are more likely to have a favorable outcome compared with preterm infants [5,7]. In addition, the severity of seizures as measured by seizure frequency, time of on-set, EEG abnormalities, and the number of AEDs used, has been associated with neurologic outcomes, especially in HIE infants [22-25].

EEG and neuroimaging findings are considered significant prognostic factors for neonatal seizures [18,26-30]. Moderate to severe background EEG abnormalities are associated with poor outcomes [8,9] and a similar result was observed in this study. Moreover, our study confirmed that the normalization of background EEG activities, especially within 3 months of a seizure or persistent normal findings on subsequent EEGs are also significant predictors of favorable outcomes ($p<0.05$). During early infancy, abnormal neurologic signs are not clearly manifested clinically except for very severe cases. Moreover, objective assessment of neurodevelopmental function is not reliable in young infants. Therefore, improvement of background EEG activities during short-term follow-up is an important predictor of favorable neurologic outcomes.

A scoring system for neurodevelopmental outcomes after seizures could be an extremely useful tool in the NICU. After the development of the first such scoring system by Ellison et al. 30 years ago [31], several other attempts have been made [18,32-34]. Unlike the previous work, the present study included both full-term and preterm neonates. Clinical variables were selected to be easily applicable at the onset of seizures and to provide accurate predictions of neurologic outcomes. In our cohort, the cutoff 3 provided a sensitivity of 84.2% and a specificity of 82.1%, with a PPV and NPV of 69.6% and 91.4%, respectively. Therefore, our scoring system could be useful in identifying infants at low risk for adverse neurologic outcomes because of its high NPV.

This study has some limitations. First, only patients with clinically evident seizures were enrolled, and thus a substantial proportion of

infants with seizures with electro-clinical dissociation apparently were likely missed. Second, it was based on a retrospective review of medical records. Therefore, diagnosis and management were not uniform in all enrolled infants and could not be generalized. Additionally, the follow-up period was not sufficient to evaluate longer-term neurologic abnormalities.

We propose using seven variables to provide early prognostic information on unfavorable neurodevelopmental outcomes in infants with neonatal seizures: birth weight, seizure onset, EEG findings, neuroimaging results, and seizure type, severity and etiology. Despite some limitations, a scoring system using these seven variables could be a useful tool in predicting neurologic outcomes. Ongoing research is needed to remedy shortcomings by prospective study applying proposed scoring system designed by this present study. In addition, EEG normalization within 3 months after seizures and persistent normal findings on subsequent EEGs are significant prognostic factors during short-term follow- up.

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