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Predictors of poor neurodevelopmental outcomes in neonates with clinically observed seizures: A prospective observational study in a tertiary care hospital of Bangladesh

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ABSTRACT

Neonatal seizures can lead to long-term neurodevelopmental problems. This study aims to identify predictors of poor developmental outcomes in neonates with seizures to aid in early intervention and referral for follow-up and rehabilitation.

This observational study was conducted in the Department of Neonatology and Institute of Paediatric Neurodisorder and Autism, Bangabandhu Sheikh Mujib Medical University. Among 75 study cases of neonatal seizure, 23 died, and 46 were followed-up at 6 and 9 months after discharge. EEGs were performed on every patient. A comprehensive neurological examination and developmental evaluation were performed using Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III).

Three-fourths of neonates were born at term (76.1 %), and over half were male (56.5 %). The majority were appropriate for gestational age (79.7 %) and had an average birth weight of 2607 ± 696 g (±SD). Over half of the neonates (52.2 %) had adverse neurodevelopmental outcomes, with global developmental delay being the most common. Recurrent seizures, the number of anticonvulsants needed to control seizures, and abnormal Electroencephalograms were identified as independent predictors of adverse neurodevelopmental outcomes.

The study highlights the need for early referral for follow-up and rehabilitation of neonates with seizures having abnormal electroencephalograms, recurrent seizures and requiring more anticonvulsants to control seizures.

1. Introduction

Neonatal seizures are a prevalent and distinctive clinical manifestation of neurologic dysfunction in the neonatal period, occurring between 1 and 5.5 per 1000 live births [1–3]. However, neonatal seizures continue to pose a clinical challenge due to their complex manifestations and the lack of evidence-based management protocols. The etiology of newborn seizures can be attributed to various factors, with hypoxic-ischemic encephalopathy, hemorrhage, intracranial infection, and metabolic abnormalities accounting for 80–85 % of all cases [4].

In the past, the mortality rate among infants who experienced seizures was as high as 40 %. However, with enhanced prenatal treatment,

Abbreviations: BSMMU, Bangabandhu Sheikh Mujib Medical University; CP, Cerebral Palsy; CPAP, Continuous Positive Airway Pressure; CSF, Cerebrospinal Fluid; EEG, Electroencephalography; GDD, Global Developmental Delay; ILAE, Internatinoal League Against Epilepsy; IPNA, Institute for Pediatric Neurodisorder and Autism.

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improved obstetric care, and intensive neonatal care, the mortality rate has decreased to 20 % in subsequent reports [5]. Nonetheless, the prevalence of long-term neurodevelopmental sequelae among survivors remains steady at 30 % [5], with newborns experiencing seizures having a higher risk of cerebral palsy, global developmental delay, and epilepsy [6].

Numerous studies have been conducted on the risk factors, causation, identification, treatment, and outcomes of neonates with seizures. The etiology of a newborn's seizure has been commonly acknowledged as playing a significant role in determining the outcome [7]. However, other markers, including brain maturity, neonatal electroencephalography (EEG) background patterns, Apgar score, and prolonged seizures, are also associated with neurodevelopmental consequences [8]. Therefore, it is crucial for neonatologists to have early and precise prognostic markers of the outcome of neonatal seizures to identify children at high risk for sequelae and intervene during the period when the central nervous system is characterized by significant plasticity [9].

Identifying risk factors that may predict the prognosis of neonates with seizures would aid in the provision of advanced care and the planning of early referrals for long-term follow-up and rehabilitation. Hence, the purpose of this study was to identify the predictors of unfavorable developmental outcomes of neonatal seizures to recommend early intervention and contribute to the current literature.

2. Methods

2.1. Study population, settings, and period

This prospective observational study was conducted in the Department of Neonatology and Institute for Pediatric Neurodisorders and Autism (IPNA) at Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh, over a period of sixteen months between June 2018 and September 2019. BSMMU is the highest-level referral center and an apex postgraduate medical institute located in the capital city of Bangladesh, Dhaka. The Department of Neonatology receives and treats patients from all around Bangladesh. However, the department lacks facilities for routine and video EEG monitoring at the bedside. Hence, management of patients is mostly based on clinical assessment. All neonates (age $\leq$ 28 days) with a diagnosis of seizures after birth were considered for inclusion. Neonates with clinically observable seizures were enrolled, while those with major congenital anomalies, those receiving cooling therapy, and those whose parents or guardians were unwilling to participate were excluded. During the enrollment period, a total of 592 neonates were admitted to the study area. Of these, 87 neonates with complaints of seizures (14.6 %), based on clinical observation and a correct description of seizure type documented in the medical records, were assessed for eligibility. Among them, six neonates were excluded because they received cooling therapy for perinatal asphyxia under the HELIX trial[10], five were excluded due to major congenital anomalies, and one patient declined to participate in the study. Finally, 75 neonates were included. Among them, 23 (30.6 %) died (18 during the hospital stay and 5 after discharge). Among the remaining neonates, 46 came for follow-up at six months, and 36 came for follow-up at nine months after delivery **(**Fig. 1**).**

2.2. Data collection tool

Data were collected using a semi-structured questionnaire. The questionnaire requested information on the sociodemographic profile and perinatal characteristics of neonates, maternal characteristics, clinical features, and investigation profile.

The first part included the age of the neonate at admission, sex, mode and place of delivery, gestational age at birth, birth weight, perinatal history including fetal growth, distress, delayed initial crying, need for resuscitation in the labor room, prolonged labor course, perinatal insult, meconium staining, and Apgar score at the 1st and 5th minute after birth.

Maternal characteristics encompassed age, education, parity, antenatal visits, presence of hypertension and/or diabetes mellitus, antenatal use of steroids or antibiotics, antepartum hemorrhage, and TORCH

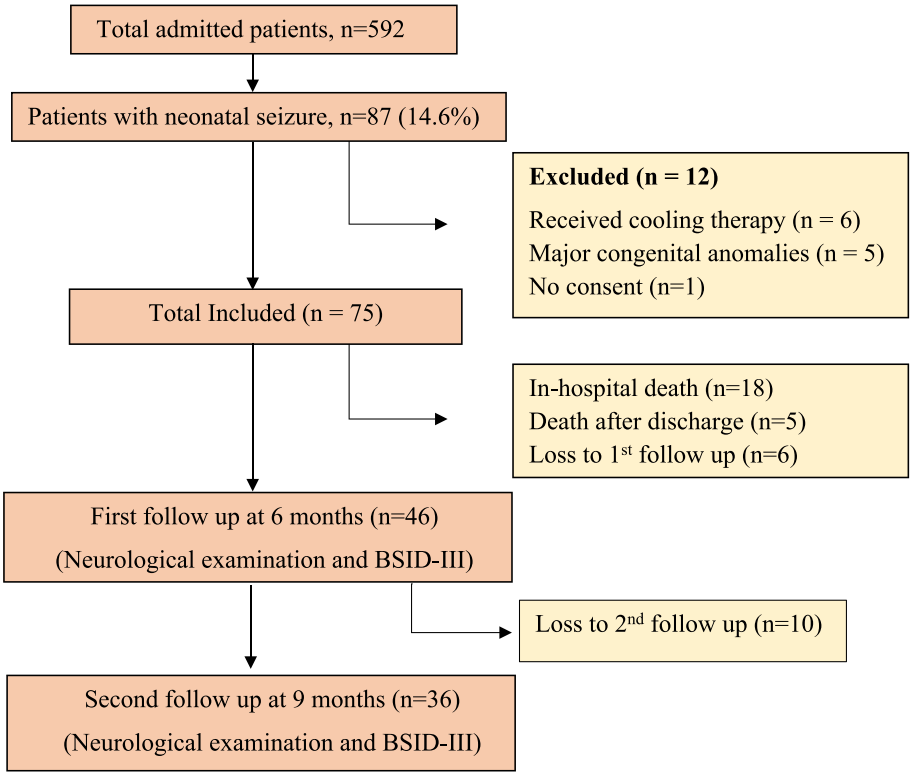

Fig. 1. Flow chart of patient enrollment and follow-up. (BSID-III: Bayley Scales of Infant and Toddler Development version III).

(Toxoplasma gondii, Rubella, Cytomegalovirus, Herpes simplex, and HIV) screening.

The clinical characteristic section recorded alertness, tone, reflexes, and occipitofrontal circumference as part of comprehensive neurological assessment, and the presence and type of seizure from medical records or direct observation.

Laboratory tests included complete blood count, cerebrospinal fluid (CSF) studies, serum glucose, electrolyte levels, blood gas analysis, Toxoplasma gondii, Rubella, Cytomegalovirus, Herpes simplex, and HIV (TORCH) screening for congenital infection or work-up for inborn errors of metabolism, cranial ultrasonography, and EEG.

2.3. Study procedure

2.3.1. At baseline

A face-to-face interview with the mother or caregivers was conducted for all enrolled newborns. The diagnosis of neonatal seizures was based on clinical observation and accurate description of seizure types documented in the medical records. It included subtle, clonic, tonic, myoclonic, and mixed-type seizures. Laboratory investigations and cranial ultrasonography were carried out as indicated to determine the primary cause of seizures. According to etiology, infants were divided into nine groups: (1) perinatal asphyxia, (2) metabolic disturbances (e.g., hypoglycemia, hypocalcemia, hyponatremia, and hypomagnesemia), (3) meningitis, (4) congenital TORCH infection, (5) intracranial hemorrhage, (6) bilirubin encephalopathy, (7) developmental cerebral defect, (8) inborn error of metabolism, and (9) unknown. When a thorough diagnostic investigation failed to identify an etiology, infants were classified as having an unknown etiology.

All patients were treated according to the standard protocol for the management of neonatal seizures. After ensuring thermal care, breathing, respiration, and circulatory support, any metabolic derangement was corrected, followed by seizure control with anticonvulsants (such as phenobarbitone, fosphenytoin, and others), and treatment of the underlying cause. Relevant data from the patient's history, physical examination, and investigations were entered into the questionnaire. Once clinically stable, an EEG was performed on every patient. EEGs were conducted in the Pediatric Neurology department of BSMMU. EEG reports were interpreted by the faculty of the Pediatric Neurology department and other neurologists when performed outside of BSMMU.

2.3.2. At follow-up

Neonates who were discharged from the hospital were followed up at 6 months and 9 months of age. All infants who attended the follow-up underwent a comprehensive neurological examination and developmental evaluation. The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III) [11], were utilized to assess development. Clinical psychologists, unaware of the patient's diagnosis, conducted this evaluation at BSMMU's Institute of Pediatric Neurodisorder and Autism (IPNA). The assessment covered cognitive development, expressive and receptive language, and fine and gross motor development using the Bayley III. A developmental delay was classified as "delayed" if any Bayley III subscale score was below 70. The outcome at follow-up was recorded as favorable (normal neurologic development) or adverse (cerebral palsy [CP], global developmental delay [GDD], and epilepsy).

2.4. Statistical analysis

Data were analyzed using Stata (version 17). Quantitative data are expressed as the mean ± SD, and categorical data are presented as proportions. All quantitative variables (between the groups of favorable and adverse outcomes) were compared using unpaired t-tests and Mann–Whitney U tests where appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. For statistical analysis, adverse outcome was defined as the development of CP, GDD, or epilepsy at six or nine months after discharge, whichever is shorter.

To determine independent predictors of adverse outcomes, multivariate logistic regression analysis was performed using variables found to be significant in univariate analysis. As the binary outcome variable showed complete separation across some predictor variables, traditional maximum likelihood would not converge. Therefore, we utilized Firth logistic regression (using the 'firthlogit' command in Stata) to mitigate small sample bias and eliminate the problem of complete separation. A p-value < 0.05 was considered significant.

2.5. Ethical measures

The study was approved by the Institutional Review Board of BSMMU (BSMMU/2018/5971). Signed informed consent was obtained from parents or caregivers before inclusion, and confidentiality was preserved. All procedures were conducted in accordance with the Declaration of Helsinki.

3. Results

The baseline characteristics of the studied neonates are presented in Table 1. A total of 23 children died during the follow-up period (33.3 %). Three-fourths of babies were born at term (76.1 %), and the majority were male (56.5 %). The mean birth weight was 2652 ± 696 g, with 20.83 % having a low birth weight. Of all, 35 (50.7 %) neonates were born by lower uterine cesarean section (LUCS). Nearly one-third of babies were delivered at home (33.3 %), and the remaining two-thirds (66.7 %) were born at the hospital. Most of them were appropriate for gestational age (AGA) (79.7 %), followed by small for gestational age (SGA) (26.1 %) and large for gestational age (LGA) (4.3 %). None of the characteristics differed significantly between those who were alive and those who were dead.

Among the 46 infants whose outcomes could be analyzed at the first follow-up, 24 (52.2 %) had adverse neurodevelopmental outcomes, and 22 (47.8 %) had normal neurological development (favorable outcome)

Table 1
Baseline characteristics of the neonates with seizure (n = 69).

Characteristics	Total n (%)	Alive n (%)	Died n (%)	p-value
n (%)	69 (100)	46 (66.7)	23 (33.3)	
Gestational age, n (%)				
Term (≥37 weeks)	55 (79.7)	35 (76.1)	20 (87.0)	0.356
Preterm (<37 weeks)	14 (20.3)	11 (23.9)	3 (13.0)	
Birth weight (gram), Mean ± SD	2607 ± 696	2652 ± 770	2490 ± 548	0.369
Sex				
Male	40 (58.0)	26 (56.5)	14 (60.9)	0.730
Female	29 (42.0)	20 (43.5)	9 (39.1)	
Mode of delivery				
Hospital	46 (66.7)	31 (67.4)	15 (65.2)	0.857
Home	23 (33.3)	15 (32.6)	8 (34.8)	
Place of birth				
Inborn	22 (31.9)	16 (34.80	6 (26.1)	0.465
Outborn	47 (68.1)	30 (65.2)	17 (73.9)	
Fetal growth at birth				
SGA	11 (15.9)	5 (10.9)	6 (26.1)	0.224
AGA	55 (79.7)	39 (84.8)	16 (69.6)	
LGA	3 (4.3)	2 (4.3)	1 (4.3)	

LUCS: Lower Uterine Caesarean section, NVD: Normal Vaginal Delivery, SGA: Small for gestational age, AGA: Appropriate for gestational age, LGA: Large for Gestational Age.

Table 2
Overall outcome of the patients with neonatal seizure (n = 46).

Type of outcome*	n (%)
Favorable outcome	22 (52.2)
Adverse neurodevelopmental outcome	22 (47.8)
CP + GDD + Epilepsy	7 (29.2)
Epilepsy only	6 (25.0)
GDD only	5 (20.8)
CP + GDD	3 (12.5)
Epilepsy + GDD	2 (8.3)
CP only	1 (4.2)

CP: Cerebral Palsy.
GDD: Global Developmental Delay.

(Table 2). Among the children with adverse outcomes, GDD (n = 19) was the most observed outcome. However, the most common outcome was the co-occurrence of CP, GDD, and epilepsy (29.2 %), followed by only epilepsy (25.0 %), only GDD (20.8 %), CP + GDD (12.5 %), epilepsy + GDD (8.3 %), and only CP (4.2 %).

When neonatal characteristics were compared between the adverse and favorable outcome groups (Table 3), home delivery (p = 0.046) and maternal prolonged labor (p = 0.018) were significantly more common among neonates with adverse outcomes. However, pregnancy-induced hypertension was significantly less common among those with adverse outcomes (p = 0.028). Other characteristics were statistically similar in relation to outcomes. Repeated episodes of seizure were significantly more common in the adverse outcome group (p = 0.001). Neonates in the adverse outcome group required additional anticonvulsants significantly more frequently than those in the favorable outcome group (p < 0.001). The median duration of injectable AEDs required was significantly longer in the adverse outcome group (p = 0.001). A significantly higher proportion of neonates with adverse outcomes had abnormal EEG findings (p < 0.001) and abnormal neurological examination at discharge (p = 0.037). However, other factors including 1st and 5th minute Apgar scores and the requirement of ventilators and continuous positive airway pressure (CPAP) were similar between the adverse and favorable outcome groups.

The independent predictors of adverse neurodevelopmental outcomes, determined by multivariate logistic regression analysis, were recurrent seizures (adjusted odds ratio [aOR]: 23.32; 95 % confidence interval [CI]: 1.31 – 416.17), the number of antiepileptic drugs (AEDs) required (aOR: 209.7; 95 % CI: 1.99 – 22061.94), and abnormal EEG findings (aOR: 67.50; 95 % CI: 1.31 – 3473.92) (Table 4).

4. Discussion

Seizures remain the most significant clinical manifestation of neurological disorders in the neonatal period. Recent advancements in newborn care are associated with a promising decline in the infant mortality rate due to neonatal seizures. We found that 33.3 % (n = 23) of newborns died at the hospital or after discharge. However, among those who survived, 52.2 % had adverse neurological outcomes at follow-up. Pisani et al. in Italy reported that a high proportion of survivors of neonatal seizures may develop long-term neurological disorders [6]. This trend may be because neonates are now surviving the acute illness, only to develop neurological complications later.

In this study, seizures were more commonly observed in males, at term, and appropriate for gestational age. However, none of these baseline parameters were significantly associated with mortality or long-term outcome. Similar to our study, male preponderance, term birth, and a high proportion of neonates appropriate for gestational age among those with seizures were reported by previous studies conducted in Bangladesh [12,13], India [14,15], and Nepal [16]. The sex difference may be attributed to male-child preference in South Asian countries, as male infants are often better cared for, and treatment for any health problems is promptly sought in many families. Neonatal seizures

Table 3
Comparison of neonatal and maternal characteristics between adverse and favorable outcome groups of neonates with seizure (n = 46).

Neonatal Characteristics	Outcome		p-value	Total
	Adverse (n = 24)	Favorable (n = 22)		n (%)
Gestational age, n (%)				
Term (≥37 weeks)	20 (57.1)	15 (42.9)	0.229	35 (76.1)
Preterm (<37 weeks)	4 (36.4)	7 (63.6)		11 (23.9)
Sex, n (%)				
Male	12 (46.2)	14 (53.8)	0.351	26 (56.5)
Female	12 (60.0)	8 (40.0)		20 (43.5)
Birth weight category (gram), n (%)				
≥ 2500	19 (79.17)	13 (59.09)	0.139	32 (69.57)
< 2500	5 (20.83)	9 (40.91)		14 (30.43)
Place of delivery, n (%)				
Home	11 (45.83)	4 (18.18)	**0.046**	15 (32.61)
Hospital	13 (54.17)	18 (81.82)		31 (67.39)
Mode of delivery				
LUCS	10 (40.0)	15 (60.0)	0.071	25 (54.3)
NVD	14 (66.7)	7 (33.3)		21 (45.7)
Fetal growth, n (%)				
SGA & LGA	3 (42.9)	4 (57.1)	0.694	7 (15.2)
AGA	21 (53.8)	18 (46.2)		39 (84.8)
Maternal Characteristics				
Parity, n (%)				
Primi	14 (66.7)	7 (33.3)	0.071	21 (45.7)
Multi	10 (40.0)	15 (60.0)		25 (54.3)
Number of ANC visits, n (%)				
< 4	7 (63.6)	4 (36.4)	0.383	11 (23.9)
≥ 4	17 (48.6)	18 (81.8)		35 (76.1)
PROM > 18 h, n (%)				
Yes	3 (60.0)	2 (40.0)	1.000	5 (10.9)
No	21 (51.2)	20 (48.8)		41 (89.1)
Antepartum hemorrhage, n (%)				
Yes	1 (33.3)	2 (66.7)	0.600	3 (6.5)
No	23 (53.5)	20 (46.5)		43 (93.5)
Intrapartum Infection, n (%)				
Yes	4 (66.7)	2 (33.3)	0.667	6 (13.0)
No	21 (55.3)	17 (44.7)		38 (82.6)

(continued on next page)

Table 3 (*continued*)

Neonatal Characteristics	Outcome		p-value	Total
	Adverse (n = 24)	Favorable (n = 22)		n (%)
TORCH infection, n (%)				
Yes		1 (20.0)	0.349	5 (10.9)
No/Unknown	20 (48.8)	21 (51.2)		41 (89.1)
Prolonged labor, n (%)				
Yes	11 (78.6)	3 (21.4)	**0.018**	14 (30.4)
No	13 (40.6)	19 (59.4)		32 (69.6)
Gestational Diabetes, n (%)				
Yes	2 (33.3)	4 (66.7)	0.405	6 (13.0)
No	22 (91.7)	18 (81.8)		40 (87.0)
Pregnancy Induced Hypertension, n (%)				
Yes	3 (25.0)	9 (75.0)	**0.028**	12 (26.1)
No	21 (61.8)	13 (38.2)		34 (73.9)
Etiology of seizure, n (%)				
PNA	16 (59.3)	11 (40.7)	0.465	27 (58.7)
Metabolic disturbance, n (%)	3 (42.9)	4 (57.1)		7 (15.2)
Meningitis	1 (25.0)	3 (75.0)		4 (8.7)
Others	2 (66.7)	1 (33.3)		3 (6.5)
Unknown	2 (40.0)	3 (60.0)		5 (10.9)
Seizure type, n (%)				
Mixed	17 (58.6)	12 (41.4)	0.298	29 (63.0)
Tonic	1 (16.7)	5 (83.3)		6 (13.0)
Subtle	4 (50.0)	4 (50.0)		8 (17.4)
Clonic	2 (66.7)	1 (33.3)		3 (6.5)
Repeated episodes of seizure, n (%)				
Yes	20 (74.1)	7 (25.9)	0.001	27 (58.7)
No	4 (21.1)	15 (78.9)		19 (41.3)
Refractory Seizure, n (%)				
Yes	4 (100.0)	0	0.110	4 (8.7)
No	20 (47.6)	22 (52.4)		42 (91.3)
Seizure Duration, n (%)				
≥30 min	3 (100.0)	0	0.235	3 (6.5)
< 30 min	21 (48.8)	22 (51.2)		43 (93.5)
Anticonvulsants required, n (%)*				
Phenobarbitone only	13 (38.2)	21 (61.8)	<0.001	34 (77.3)
Phenobarbitone plus additional AEDs	10 (43.5)	0		10 (22.7)
Duration of injectable AED in days, median (IQR)	9 (3 – 15)	1 (1 – 3)	0.001	5 (1 – 9.75)
AED on discharge, n (%)				
Yes	13 (92.9)	1 (7.1)	<0.001	14 (30.4)
No	11 (34.4)	21 (65.6)		32 (69.6)
1 min Apgar, n (%)*				
≤ 3	3 (60.0)	2 (40.0)	0.326	5 (20.8)
> 3	6 (31.6)	13 (68.4)		19 (79.2)
5 min Apgar, n (%)*				
≤ 3	3 (75.0)	1 (25.0)	0.090	4 (16.7)
> 3	6 (30.0)	14 (70.0)		20 (83.3)
EEG findings, n (%)				
Abnormal	12 (92.3)	1 (7.7)	<0.001	13 (28.3)
Normal	12 (36.4)	21 (63.6)		33 (71.7)
Neurological Examination at discharge, n (%)				
Abnormal	17 (68.0)	8 (32.0)	0.037	25 (54.3)
Normal	7 (33.3)	14 (66.7)		21 (45.7)
Ventilator, n (%)				
Yes	2 (66.7)	1 (33.3)	1.000	3 (6.5)
No	22 (51.2)	21 (48.8)		43 (93.5)
CPAP, n (%)				
Yes	5 (71.4)	2 (28.6)	0.418	7 (15.2)
No	19 (48.7)	20 (51.3)		39 (84.8)

Statistical test: Independent *t*-test, Mann-Whitney *U* test, Chi square test & Fisher's Exact test as appropriate.

AED: Anti-epileptic Drug; AGA: Appropriate for Gestational Age; CPAP: Continuous Positive Airway Pressure; EEG: Electroencephalogram; LGA: Large for Gestational Age; PNA: Perinatal asphyxia; SD: Standard Deviation; SGA: Small for Gestational Age; *Based on available data.

frequently occur in premature infants [17]. However, this study observed a predominance of term newborns with birth weights appropriate for gestational age who had seizures. These results agreed with a previous cohort from Bangladesh and other studies from neighboring countries [14,17,18].

On bivariate analysis, we found that home-born neonates were significantly more likely to have adverse neurodevelopmental outcomes, indicating a lack of skilled birth attendant at home. This is similar to the findings of a large study conducted in the United States [19]. However, we noted that delivery place became nonsignificant after adjustment for other factors, especially seizure-related factors, associated with adverse outcomes, highlighting the importance of the severity of seizures in developing long-term complications. Similarly, prolonged labor, found to be significant on bivariate analysis, became nonsignificant in multivariable regression. However, different causes of prolonged labor have been reported to be associated with cerebral palsy [20] and neurodevelopmental delay [21]. Prolonged labor might predispose patients to seizures by causing birth asphyxia [22]. In line with this evidence, we found that perinatal asphyxia was the most common cause of neonatal

Table 4
Predictors associated with adverse neurodevelopmental outcome by multivariate logistic regression analysis.

Predictors	Reference Category	Adverse neurodevelopmental outcome	
		OR (95 % CI)	p-value
Place of delivery (Home)	Hospital	3.48 (0.30 – 39.93)	0.315
Prolonged labor (Yes)	No	0.03 (0.00 – 4.65)	0.175
Maternal HTN (Present)	Absent	0.69 (0.06 – 8.26)	0.768
Recurrent Seizure (Yes)	No	23.32 (1.31 – 416.17)	**0.032**
AED required to control seizure (Phenobarbitone + Additional)	Phenobarbitone only	209.7 (1.99 – 22061.94)	**0.024**
Duration of injectable AED (Days)		0.94 (0.76 – 1.15)	0.525
Neurological examination at discharge (Abnormal)	Normal	0.58 (0.04 – 8.24)	0.687
EEG (Abnormal)	Normal	67.50 (1.31 – 3473.92)	**0.036**
AED required at discharge (Yes)	No	1.20 (0.08 – 17.05)	0.893

AED: Antiepileptic drugs; HTN: Hypertension; EEG: Electroencephalogram.
Statistical test: Binary logistic regression
OR: Odd ratio, CI: Confidence Interval.

seizures, which is in agreement with other studies [14–16,23,24]. Additionally, concordant with the findings of Das et al. in India [23] and Singh et al. in Nepal [16], meningitis was the second most common cause of seizures found in this study. Some studies have suggested that the etiology of neonatal seizures is the most important factor influencing outcome [8,25]. However, we did not find a statistical relationship between seizure etiology and outcome, a finding reported previously by Pisani et al. [8] and Lai et al. [26]. Similarly, in concordance with Tekgul et al. [5], we did not find any association between seizure type and outcome.

In this study, the predominant type of seizure was mixed type, whereas studies by Lai et al. in Taiwan [26], Bagla et al. in India [14], and Amare & Amare in Ethiopia [27] reported that subtle seizures were the main type in their study. There are two possible explanations for these differences. One, these studies could have reported the non-overlapping frequencies of different types of seizures, while we reported combined frequency, making the isolated incidence of subtle type lower in this study. Two, as subtle seizures are often missed clinically due to their mimicry with normal behavior and can only be clearly captured using video EEG [27], our study might have missed the subtle types due to the absence of continuous video EEG monitoring in the context of low-resource settings.

This study found no significant relationship between the predominant clinical seizure type and outcome, which was consistent with the finding of Tekgul et al. [5]. However, on multivariable analysis, we found that the frequency of seizures, severity of seizures (as determined by the number of antiepileptic drugs required to control), and presence of abnormal electrical activity in the EEG were significant predictors of adverse neurodevelopmental outcomes among our sample.

Repeated seizures have been documented as a predictor of adverse outcomes in other studies [6]. Studies in rats have shown that repeated neonatal seizures result in reduced spike frequency adaptation and long-term selective impairment in GABAergic neurotransmission of the hippocampus [28], probably contributing to enhanced long-term seizure susceptibility [29]. The present study supports the evidence that repeated seizure episodes during the neonatal period may act on an epileptogenic substrate and are responsible for subsequent adverse neurodevelopmental outcomes. EEG background findings were documented as predictors in neonatal seizures by different studies [5,15,17,26], which is compatible with our findings.

Our study did not find any association of neonatal seizure outcomes with the Apgar score at 1st or 5th minute after delivery, which is discordant with previous studies [6,24]. The most likely cause might be that Apgar score documentation was not present in less than half of the cases. Particularly, in countries with a high percentage of home delivery, the Apgar score might be unavailable and, hence, cannot be used as a predictor of outcome.

4.1. Limitations and strengths

The limitations of this study included the small sample size and a lack of long-term follow-up. Additionally, the diagnosis of seizures relied primarily on clinical history and examination rather than video EEG due to resource limitations. The International League Against Epilepsy (ILAE) 2021 classification of neonatal seizures emphasizes the role of EEG in diagnosing and classifying seizures. In a low-resource setting where EEG monitoring is not available, this classification is not possible. Hence, for our patients, it was not feasible to classify seizures according to ILAE guidelines. However, this study is one of the few that explored long-term outcomes in infants with neonatal seizures in the context of low-resource settings, thus contributing to the existing knowledge base.

4.2. Conclusions

Repeated episodes of seizures, abnormal EEG, and the requirement for more than one antiepileptic drug to control seizures are significant predictors of adverse neurodevelopmental outcomes in patients with neonatal seizures. Clinicians should consider these factors during discharge and ensure regular follow-up and drug compliance in infants at higher risk of adverse neurodevelopmental outcomes.

4.3. Recommendations

Based on the study findings, we have the following recommendations regarding the management and follow-up of neonatal seizures:

1. In low-resource settings where continuous EEG monitoring is not possible, an EEG should be performed for all neonates with seizures before discharge to predict adverse outcomes early.
2. Neonates with a history of repeated seizures and requiring more than one anticonvulsant to control seizures should be referred early for long-term neurodevelopmental follow-up and rehabilitation.

CRediT authorship contribution statement

Humayra Akter: Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Sanjoy Kumer Dey:** . **Mohammad Kamrul Hassan Shabuj:** Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Data curation, Conceptualization. **Kanij Fatema:** Visualization, Validation, Software, Methodology, Investigation, Data curation, Conceptualization. **Ismat Jahan:** Writing – original draft, Validation, Software, Resources, Investigation, Data curation, Conceptualization. **Nazmus Sihan:** Writing – original draft, Visualization, Supervision, Investigation, Funding acquisition, Conceptualization. **Tareq Rahman:** Writing – original draft, Validation, Software, Resources, Methodology, Data curation, Conceptualization. **Md Abdullah Saeed Khan:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Mohammad Jahid Hasan:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data is available upon reasonable request from the corresponding author.

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Use of AI (ChatGPT)

We used ChatGPT 3.5 for grammatical correction.

References

[1] Lanska MJ, Lanska DJ, Baumann RJ, Kryscio RJ. A population-based study of neonatal seizures in Fayette County. Kentucky Neurology 1995;45(4):724–32. https://doi.org/10.1212/wnl.45.4.724.
[2] Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. J Pediatr 1999;134(1):71–5. https://doi.org/10.1016/s0022-3476(99)70374-4.
[3] Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. Semin Fetal Neonatal Med 2013;18(4):185–91. https://doi.org/10.1016/j.siny.2013.05.008.
[4] Kang SK, Kadam SD. Neonatal seizures: impact on neurodevelopmental outcomes. Front Pediatr 2015;3:101. https://doi.org/10.3389/fped.2015.00101.
[5] Tekgul H, Gauvreau K, Soul J, Murphy L, Robertson R, Stewart J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics 2006;117(4):1270–80. https://doi.org/10.1542/peds.2005-1178.
[6] Pisani F, Spagnoli C. Neonatal seizures: a review of outcomes and outcome predictors. Neuropediatrics 2015;47(1):12–9. https://doi.org/10.1055/s-0035-1567873.
[7] Krawiec C, Muzio MR. Neonatal seizure [Accessed 2023 March 19] Stat Pearls 2022. https://www.ncbi.nlm.nih.gov/books/NBK554535/.
[8] Pisani F, Facini C, Pelosi A, Mazzotta S, Spagnoli C, Pavlidis E. Neonatal seizures in preterm newborns: a predictive model for outcome. Eur J Paediatr Neurol 2016;20(2):243–51. https://doi.org/10.1016/j.ejpn.2015.12.007.
[9] Soltirovska-Salamon A, Neubauer D, Petrovcic A, Paro-Panjan D. Risk factors and scoring system as a prognostic tool for epilepsy after neonatal seizures. Pediatr Neurol 2014;50(1):77–84. https://doi.org/10.1016/j.pediatrneurol.2013.08.010.
[10] Thayyil S, Oliveira V, Lally PJ, Swamy R, Bassett P, Chandrasekaran M, et al. Hypothermia for encephalopathy in low and middle-income countries (HELIX): study protocol for a randomised controlled trial. Trials 2017;18(1):432. https://doi.org/10.1186/s13063-017-2165-3.
[11] Bayley N, Scales B. of infant and toddler development. Third Edition. Pearson; 2005 [Accessed 2023 March 19].
[12] Parvin R, Salim A, Rahman M, Chowdhury K, Sultana A, Ahmed S, et al. Neonatal seizures: Correlation between clinico-etiological profile and EEG findings. Bangladesh J Child Heal 2014;38(1):19–23. https://doi.org/10.3329/bjch.v38i1.20023.
[13] Ara R, Uddin M. Determinants of neonatal seizures among newborns attending in a Tertiary Care hospital. JAFMC Bangladesh 2014;10:1–8.
[14] Bagla J, Garg H, Gulati RK, Gupta PP. Clinicoetiology profile of neonatal seizures in Tertiary Care level ii neonatal intensive Care unit. indian J child. Health 2017;04(3):383–6. https://doi.org/10.32677/IJCH.2017.v04.i03.026.
[15] Kolkar YB, Sailavasan M. A prospective study to determine etiology, clinical profile and neurodevelopmental outcome of neonatal seizures admitted in newborn unit of Chengalpattu medical college and hospital, Tamil Nadu. India Int J Contemp Pediatr 2019;6(2):527–34. https://doi.org/10.18203/2349-3291.ijcp20190688.
[16] Singh SD, Shrestha RPB, Shrestha A. Etiological profile and neurodevelopment outcome of neonatal seizure. J Lumbini Med Coll 2018;6:1–33.
[17] Nunes ML, da Costa JC. Outcome of newborns with neonatal seizures: risk factors and predictors. Curr Pediatr Rev 2006;2(4):315–21. https://doi.org/10.2174/157339606778699662.
[18] Kumar A, Gupta A, Talukdar B, Kumar A. Clinico-etiological and EEG profile of neonatal seizures. Indan J Pediatr 2007;74(1):33–7. https://doi.org/10.1007/s12098-007-0023-0.
[19] Grünebaum A, McCullough LB, Sapra KJ, Brent RL, Levene MI, Arabin B, et al. Apgar score of 0 at 5 minutes and neonatal seizures or serious neurologic dysfunction in relation to birth setting. Am J Obstet Gynecol 2013;209(4):1–323.
[20] Anwar S, Chowdhury J, Khatun M, Mollah AH, Begum HA, Rahman Z, et al. Clinical profile and predisposing factors of cerebral palsy. Mymensingh Med J 2007;15(2):1–86. https://doi.org/10.3329/mmj.v15i2.32.
[21] Chebet M, Musaba MW, Mukunya D, Makoko B, Napyo A, Nantale R, et al. High burden of neurodevelopmental delay among children born to women with obstructed labour in eastern Uganda: a cohort study. Int J Environ Res Public Health 2023;20(4):1–11. https://doi.org/10.3390/ijerph20043470.
[22] Abdo RA, Halil HM, Kebede BA, Anshebo AA, Gejo NG. Prevalence and contributing factors of birth asphyxia among the neonates delivered at nigist eleni Mohammed memorial teaching hospital, southern Ethiopia: a cross-sectional study. BMC Pregnancy Childbirth 2019;19(1):1–7. https://doi.org/10.1186/s12884-019-2696-6.
[23] Das D, Debbarma SK. A study on clinical profile of neonatal seizures. J 2018;5(7):95–101. https://doi.org/10.21276/ijcmr.2018.5.7.12.
[24] Anand V, Nair PMC. Neonatal seizures: predictors of adverse outcome. J Pediatr Neurosci 2014;9(2):97–9. https://doi.org/10.4103/1817-1745.139261.
[25] Scher MS. Diagnosis and management of neonatal seizures. by eli M. mizrahi and Peter kellaway Philadelphia, lippincott-raven, illustrated. Ann Neurol 1998;44(6):988. https://doi.org/10.1002/ana.410440628.
[26] Lai YH, Ho CS, Chiu NC, Tseng CF, Huang YL. Prognostic factors of developmental outcome in neonatal seizures in term infants. Pediatr Neonatol 2013;54(3):166–72. https://doi.org/10.1016/j.pedneo.2013.01.001.
[27] Amare HT, Amare AT. Etiology, clinical features, and short-term outcome of seizures in newborns admitted to the University of Gondar Hospital. Ethiopia Pediatr Heal Med Ther 2019;10:107–13. https://doi.org/10.2147/PHMT.S228241.
[28] Villeneuve N, Ben-Ari Y, Holmes GL, Gaiarsa JL. Neonatal seizures induced persistent changes in intrinsic properties of CA1 rat hippocampal cells. Ann Neurol 2000;47(6):729–38.
[29] Isaeva E, Isaev D, Savrasova A, Khazipov R, Holmes GL. Recurrent neonatal seizures result in long-term increases in neuronal network excitability in the rat neocortex. Eur J Neurosci 2010;31(8):1446–55. https://doi.org/10.1111/j.1460-9568.2010.07179.x.