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Predictors of Adverse Outcomes in Neonates with Seizures

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Abstract: Background: Seizures in neonatal period could generate long-term neurodevelopmental impairment; therefore, explicit clarification of adverse outcome predictors should direct the ongoing and subsequent treatment plan. Objective: The study aimed to address predictors of adverse neurodevelopmental outcomes and/or mortality of full-term infants who developed neonatal seizures. Methods: This longitudinal prospective cohort study was conducted from 2019 to 2021 in tertiary hospital, Egypt and included the full-term infants till 18 months of age after occurrence of clinical/electrical seizures in neonatal period and healthy infants of matched age and sex. All infants were assessed by Bayley-III developmental scales in three main domains (cognitive, language and motor). The required data for the predictive factors of adverse outcome had been registered on REDCap tools and exported for statistical analysis. Results: Sixty four infants were enrolled (35 developed seizures and 29 were healthy), 29% died. There were significant group differences (better results were in favor of healthy infants) in the need for initial resuscitation, 1st and 5th minute APGAR score and in all developmental domains. Medium correlation was found between abnormal motor subscale and multiple attacks of seizures, the need for anti-seizure medication on discharge and low 5th minute APGAR score. Time to death was significant earlier in infants required initial resuscitation, developed seizures within 1st day of life with special characteristics (as exceeding 6 days with abnormal aEEG background, >2 anti-epileptic drugs were prescribed for optimum control and also were prescribed on their discharge plan) and also those exceeded 19 days admission in NICU. Conclusion: Occurrence of seizures in neonatal period had its unique signature on long-term morbidity. Early death and abnormal motor domain in later life could be predicted from the 1st days of birth though low APGAR score, frequency and duration of seizures, EEG background and the need for anti-seizure medication on discharge.

Keywords: APGAR Score, Cognitive, Language, Seizures

1. Introduction

Seizures are critical neurological events in newborn [1]. The major etiology of neonatal acute brain injury is hypoxic-ischemic encephalopathy (HIE). Other contributing etiologies as acute stroke, intracranial hemorrhage (ICH), CNS infection as well as electrolyte disorders. Establishing correct diagnosis and implementing distinct treatment are the cornerstone to limit adverse long-term morbidity and improve outcomes of neonatal seizures [1].

Neonatal seizures are common contributors for death and abnormal development [2]. Though, mortality has reduced from 40% to 20%, prevalence of long-standing neurodevelopmental sequelae is almost the same at 30% [3]. Among survivors; adverse neurodevelopmental sequelae are cerebral palsy, developmental delay, and post-neonatal epilepsy [4]. Of note, burden of acute recurrent seizures in neonates may also impact chronic outcomes independent of the etiology [5]. In contrary, even short event may signify serious underlying problem that occur in immature brain [6].

Neurobehavioral assessment in newborns is a challenging task as they have complicated growing cerebral functions affecting their neurological development as tone, reflexes and cognitive abilities. The ideal assessment is achieved by explicit and clear awareness of multiple faces of development and availability of accurate assessment tools [7]. Baylay scales of infant development (BSID) are used popularly for neurodevelopmental assessment of infants and toddlers [8].

BSID scored 5 subscales: cognitive, language, motor, social-emotional and adaptive-behavioral subscales. Surprisingly, many studies reported long-term neurodevelopmental outcome of infants with neonatal seizure at different postnatal ages using BSID [9-13] but none of these studies demonstrated healthy infants as a control group. Therefore, we aimed to address the neurodevelopmental outcome at 18 months of age for exposed and non-exposed infants to acute adverse brain event and to find out etiological factors and predictors of worse outcomes.

2. Methods

We performed a single-center prospective cohort study in tertiary hospital, Egypt over 2 years. Informed consents were obtained from all caregivers of patients and healthy group before inclusion in the study and after assuring confidentiality. Approval by medical research ethics committee of Mansoura Faculty of Medicine was obtained at September, 2019. We included the full-term infants who developed clinical seizures in the 1st 28 days of life (in the form of tonic, clonic, myoclonic or subtle focal, multifocal or bilateral, either single or multiple attacks) and those with abnormal electrical activity detected by amplitude integrated EEG (aEEG) (NicoletOne machine was used). Six Electrodes were placed using international 10/20 system [14] and applied for 48 hours in suspected neonates. Whenever seizures were documented, the infants were monitored for 24 hours. Seizure is diagnosed as a transient rise in amplitude, maximum and minimum border [15]. We excluded babies having congenital brain malformation and babies died or lost follow up prior to the end of study. Etiological categorization was done after full clinical, laboratory and radiological assessment into: HIE, focal cerebral ischemia, trauma/hemorrhage, metabolic disturbances (hypoglycemia, hypocalcemia, and kernicterus), CNS infection, metabolic/genetic and idiopathic.

Neurodevelopmental outcome: All survivors and healthy group were followed-up at 18 months of life in dedicated clinic for high risk newborn. They were assessed by BSID-III. Death prior to 18 months of age or deviation of composite score of developmental scale more than two SD below the mean are defined as adverse outcome.

Instruments: Bayley-III was performed by licensed examiner over 60-90 minutes. Raw scores from the cognitive scale were converted to composite scores equivalent (range 55- 145, mean =100±15). Raw scores of receptive and expressive communication subtests were converted to scaled score. Scaled score of language scale was converted to composite score (range 47-153), the same for raw scores of fine and gross motor subtests. Scaled score of motor scale was converted to composite score (range 46-154). Infants that were untestable with the BSITD-III, were assigned lowest scores in all domains. The Bayley-III has not been standardized in Egypt; accordingly, the USA norms of scales were used in current study. Therefore, an index composite Bayley score of < 70 is defined to indicate severe impairment [8, 16].

Data were collected using *REDCap* (research electronic data capture) tools [17]. The collected data was analyzed using SPSS Ver.22 using appropriate statistical tests. Qualitative data was analyzed using chi-square or fischer exact test. Quantitative data was described as median (min-max) using Mann-Whitney test. Odds ratio and their 95 confidence interval was calculated. P value was statistically significant if ≤0.05.

3. Results

Over the 24-month study period, 170 high risk full-term infants for seizures were admitted to NICU. Of these, we excluded 112 infants from the study based on our entry criteria as 39 of them had major brain anomalies and 73 didn't develop either clinical or electrical seizures. Nine of the remaining term infants died during the acute neonatal illness. Eight infants died during follow-up period and 6 were lost to follow-up, precluding reliable long-term evaluation. We followed 34 healthy infants at same time, 5 of them lost their follow-up visits. The study therefore focused on the 29 healthy infant (15 girls and 14 boys) and surviving 35 term infants (16 girls and 19 boys) with seizures in the newborn period who were subsequently divided into two groups: 30 infants with clinical seizures (Cz=30) and 28 infants with either electrical seizures (Ez=4) and/or electro-clinical seizures (ECz=24), all of them were followed in our NICU clinic at 18 months of age (as shown in figure 1). Table 1 showed that diseased infants required initial resuscitation, achieved lower APGAR scores at 1 and 5 min at a significant higher level than healthy group. Birth weight of survived infants ranged from 1500 to 4200 grams.

Table 2 showed that the onset of 1st event was a significant earlier in infants with abnormal electrical activity vs. those with clinical events; moreover, myoclonic and subtle events occurred at a significant higher frequency in the former group. Distribution of the predominant clinical type among survivors was as follows: clonic [39%], tonic [26%], myoclonic [13%], tonic-clonic [16%] and subtle [6%]. Fifty three of neonates with seizures received anti-seizure medications (ASMs) at time of admission, 28 of them were discharged on ASMs.

Table 3 showed that that HIE was the most common cause of seizures among our cases, followed by CNS infection, hemorrhage and stroke. Nearly 38% of infants had more than one etiology. Abnormal electrical discharges were more recorded in HIE infants, while clinical seizures were more noticed in infants with stroke. Table 4 showed a significant lower developmental scores of all domains in the infants developed seizures vs. healthy group. Moreover, the rates of developmental cognitive impairment were 30%, language impairment 50% and motor impairment 58.3% in infants with seizures. Table 5 showed a medium strength of significant correlation between abnormal motor subscale and the frequency of seizures, medications on discharge and low 5th min APGAR score.

Table 6 showed that survival distributions (time to death) were statistically significant earlier for infants admitted within 1st DoL (day of life) vs. those admitted after 1st DoL (figure 2), infants required initial resuscitation, MV (mechanical ventilation) (figure 3) and HFOV (high

frequency oscillation ventilation) vs. those didn't require these maneuvers, infants started >2 antiepileptic drugs (AEDs) to stop initial seizures and discharged on AEDs (figure 4) vs. those started <2 drugs and discharged without medication, infants showed severe abnormal aEEG background vs. those with moderate background and infants admitted >19 days and seizure duration (clinical or electrical) exceeded 6 days vs. those admitted for shorter period and seizure duration was shorter (figure 5).

Table 1. *Clinical characteristics in studied groups.*

Characteristic	Diseased (N=58)	Control (N=34)	P value
Categorical	**N (%)**		
Sex			
Female	25 (43.1%)	17 (50%)	0.522*
Male	33 (56.9%)	17 (50%)	
Mode of delivery			
CS	30 (51.7%)	23 (67.6%)	0.209$
Vaginal	16 (27.6%)	10 (29.4%)	
Others$	12 (20.7%)	1 (2.9%)	
Multiple birth	3 (5.2%)	3 (8.8%)	0.666$
Delivery room resuscitation	40 (69%)	0 (0%)	**<0.001***
Quantitative (numeric)	Median (min-max)		
Gestational age (weeks)	38 (37-39)	38 (37-39)	0.864
Birth weight (gram)	3200 (2875-3600)	3200 (3000-3500)	1
Birth length (cm)	50 (48-50)	50 (49-51)	0.331
Birth HC (cm)	35 (33-36)	35 (34-36)	0.397
Maternal age (years)	30 (25-32)	30 (25.7-32)	0.954
Gravidity	3 (1-4)	3 (2-3)	0.868
Parity	3 (1-3)	2.5 (2-3)	0.690
Number of living children	2 (1-3)	2.5 (2-3)	0.105
APGAR score at 1 min	3.5 (2-6)	10 (9-10)	**<0.001**
APGAR score at 5 min	5 (4-7)	10 (10-10)	**<0.001**

Test of significance is *Chi-square or $Fisher's exact test for categorical data and Mann Whitney test for quantitative data. $ Other modes of delivery include spontaneous, ventouse and forceps delivery. CS; caesarian section, HC; head circumference

Table 2. *Characteristics of seizures in studied cases.*

Characteristic	Cz (N=30)	Ez/ECz (N=28)	P value
	N (%)		
Type of seizures			
Tonic	10/30 (33.3%)	4/24 (16.7%)	
Clonic	9/30 (30%)	7/24 (29.2%)	0.045$
Myoclonic	4/30 (13.4%)	7/24 (29.2%)	
Subtle	0/30 (0%)	4/24 (16.6%)	
Tonic-clonic	7/30 (23.3%)	2/24 (8.3%)	
Localization of Cz			
Focal	10/30 (33.3%)	2/20 (10%)	0.188$
Multifocal	11/30 (36.7%)	9/20 (45%)	
Generalized	9/30 (30%)	9/20 (45%)	
Frequency Cz			
Single	4/30 (13.3%)	0/24 (0%)	0.120$
Multiple	26/30 (86.7%)	24/24 (100%)	
Number of AEDs stop seizures			
0	4/30 (13.3%)	1/28 (3.6%)	0.158$
≤2	17/30 (56.7%)	14/28 (50%)	
>2	9/30 (30%)	13/28 (46.4%)	
AEDs on discharge	16/29 (55.2%)	12/20 (60%)	0.737*
aEEG status epilepticus		8/28 (28.6%)	
Median (min-max)			
Onset of 1st Cz (days)	4 (1-6.25)	1 (1-2)	<0.001
Age of seizure control (days)	9 (6.75-19.25)	7.5 (5.25-15)	0.197
Duration of Cz (days)	6 (1-11)	5.5 (3-13)	0.422
Duration of aEEG placement (days)		7 (4-11)	

Test of significance is *Chi-square or $Fisher's exact test for categorical data and Mann Whitney test for quantitative data. Abbreviation, aEEG, amplitude integrated EEG, AEDs, anti-epileptic drugs, Cz; clinical seizures, ECz; electro-clinical seizures, Ez; electrical seizures.

Table 3. *Etiology of seizures studied cases.*

Cause	Cz	Ez/ECz	P value
HIE			
Moderate	5 (16.7%)	12 (42.9%)	0.006*
Severe	5 (16.7%)	9 (32.1%)	
Stroke	6 (20%)	0 (0%)	0.024$
Hypoglycemia	5 (16.7%)	3 (10.7%)	0.707$
Hypocalcemia	2 (6.7%)	0 (0%)	0.492$
ICH	7 (23.3%)	2 (7.1%)	0.147$
CNS infection	11 (36.7%)	7 (25%)	0.337*
Metabolic/genetic	1 (3.3%)	5 17.9%)	0.097$
Kernicterus	4 (13.3%)	0 (0%)	0.113$
Idiopathic	0 (0%)	1 (3.6%)	0.483$

Data is N (%). Test of significance is *Chi-square or $Fisher's exact test. Abbreviation, CNS; central nervous system, Cz; clinical seizures, ECz; electro-clinical seizures, Ez; electrical seizures, HIE; hypoxic ischemic encephalopathy, ICH; intracranial hemorrhage.

Table 4. *Developmental scores in the studied groups at 18 months.*

Parameters /Time	Diseased (35)	Control (29)	P	Rate of impairment
Composite score	Median (min-max)			N (%)
Cognitive	75 (65-80)	125 (117.5-135)	<0.001	11 (30.6)
Language	69.5 (62.7-83)	118 (109-124)	<0.001	18 (50)
Motor	64 (58.7-82)	127 (118-134.5)	<0.001	21 (58.3)

Test of significance is Mann Whitney test

Table 5. *Correlation between abnormal developmental scores and other predictors.*

Bayley III	Cognitive		Language		Motor	
APGAR score at 5 min						
< 5	7		9		13	
≥ 5	4		9		8	
	P	Phi	P	Phi	P	Phi
	0.14$	-0.29	0.5*	-0.16	0.006*	-0.48
Frequency of seizures						
Multiple	9		18		20	
Single	0		0		0	
	0.3$	0.23	0.028$	0.43	0.014$	0.48
AED on discharge						
Yes	5		11		14	
No	6		7		7	
	1*	-0.02	0.18*	0.27	0.008*	0.46

Data is N. Test of significance is *Chi square test of association or $Fischer exact test. Phi is a measure of strength of association. Abbreviation, AED; anti-epileptic drug, Cz; clinical seizures, ECz; electro-clinical seizures, Ez; electrical seizures.

Table 6. *Factors affecting time to death (months) in studied cases.*

Factor	Total N	N (%) of events	Median (95% CI)	Log-rank test	
				$\chi 2$	P value
Admission age (days)					
≤1 day	38	14 (37%)	NA (NA-NA)	4.009	0.045
>1 day	20	3 (15%)	NA (NA-NA)		
Need for initial resuscitation					
No	18	1 (5%)	NA (NA-NA)	7.134	0.008
Yes	40	16 (40%)	NA (NA-NA)		
Need for MV					
No	27	2 (7%)	NA (NA-NA)	13.623	<0.001
Yes	31	15 (48%)	12 (NA-NA)		
Need for HFOV					
No	49	10 (20%)	NA (NA-NA)	33.9	<0.001
Yes	9	7 (78%)	1 (0.6-1.4)		
Numbers of AED to stop seizures					
0-2 drugs	36	6 (17%)	NA (NA-NA)	10.169	0.001
>2 drugs	22	11 (50%)	9 (NA-NA)		
AED prior to discharge					
No	21	1 (5%)	NA (NA-NA)	4.241	0.039
Yes	28	7 (25%)	NA (NA-NA)		

Factor	Total N	N (%) of events	Median (95% CI)	Log-rank test	
				$\chi 2$	P value
Abnormal aEEG background					
Moderate	16	4 (25%)	NA (NA-NA)	6.442	0.011
Severe	9	6 (67%)	1 (0.63-1.36)		
Duration of Cz (days)					
≤6 days	32	6 (19%)	NA (NA-NA)	6.097	0.014
>6 days	22	11 (50%)	18 (NA-NA)		
Seizure period of Ez (days)					
≤6 days	18	2 (11%)	NA (NA-NA)	15.267	<0.001
>6 days	10	8 (80%)	1 (0.58-1.4)		
Length of hospital stay (days)					
≤19 days	30	3 (10%)	NA (NA-NA)	10.625	0.001
>19 days	28	14 (50%)	18 (NA-NA)		
Therapeutic hypothermia					
No	50	17 (34%)	6 (1.8-10.1)	3.473	0.06
Yes	8	0 (0%)	NA (NA-NA)		
Etiology of seizures					
HIE	31	12 (39%)	NA (NA-NA)	3.435	0.06
Stroke	6	1 (17%)	NA (NA-NA)	0.621	0.431
ICH	9	3 (33%)	NA (NA-NA)	0.013	0.909
Infection	18	6 (33%)	NA (NA-NA)	0.240	0.624
Hypoglycemia	8	2 (25%)	NA (NA-NA)	0.201	0.654

NA=Not available (50% cumulative survival was not attained). Abbreviation, AED; anti-epileptic drug, aEEG, amplitude integrated EEG, CI=confidence interval, Cz; clinical seizures, ECz; electro-clinical seizures, Ez; electrical seizures, HFOV; high frequency oscillation ventilation, HIE; hypoxic ischemic encephalopathy, ICH, intracranial hemorrhage, MRI; magnetic resonance imaging, MV; mechanical ventilation.

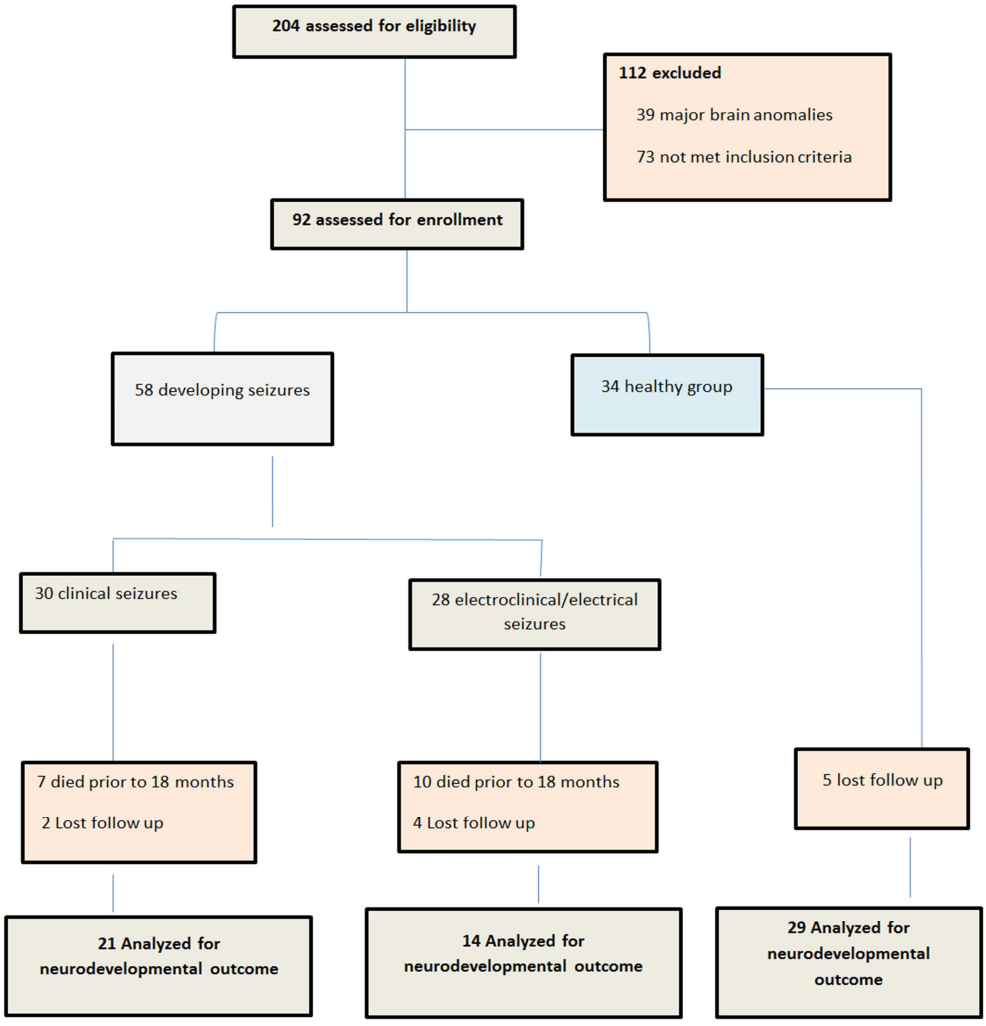

Figure 1. *Flowchart of the studied groups.*

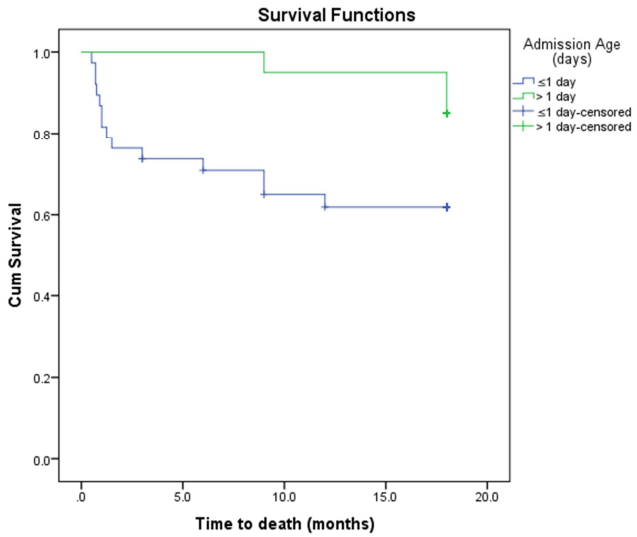

Figure 2. *Effect of admission age on time to death.*

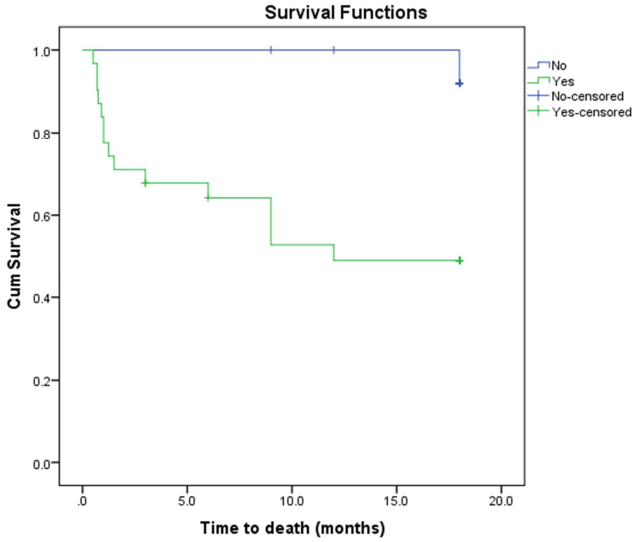

Figure 3. *Effect of mechanical ventilation on time to death.*

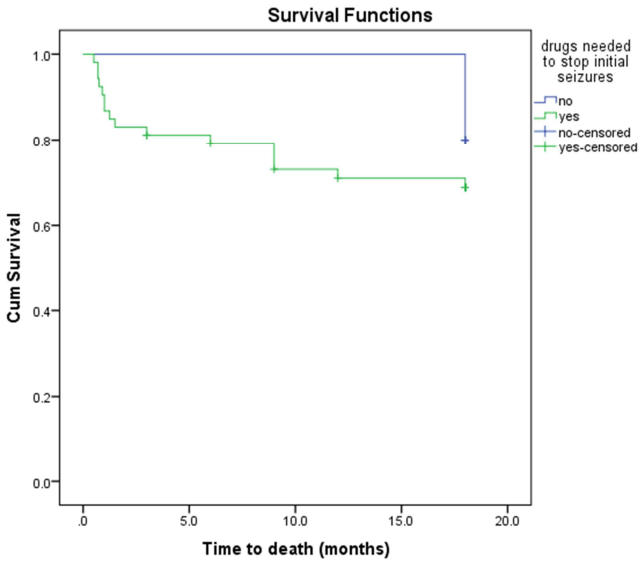

Figure 4. *Effect of number of AEDs controlling seizure on time to death.*

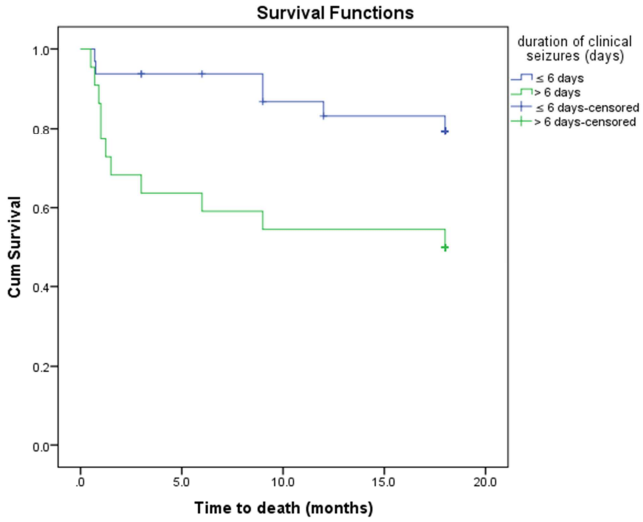

Figure 5. *Effect of seizure duration on time to death.*

4. Discussion

We conducted a longitudinal prospective cohort study on 35 survived full term infants who developed clinical or electrical seizures in neonatal period and 29 healthy infants measuring the neurodevelopmental motor, cognitive and language domains at age of 18 months. We found a significant reduction of all domains in infants with seizures with subsequent selective clarification of predictors for occurrence of early death and poor motor performance.

It is a fully understood fact that some perinatal factors such as need for resuscitation, Apgar scores [18-23] are related to neonatal seizures. Our cohort showed that infants developed seizures were predominantly males (57%) and most of them required initial resuscitation, and achieved lower APGAR scores at 1 and 5 min at a significant higher level than healthy group. Some studies [9, 24, 25] also demonstrated male predominance among infants with neonatal seizures.

Variability in clinical presentation of neonatal seizures is the major factor for either over-diagnosis (excessive abnormal movement as jitteriness, startle) or under-diagnosis (presence of electrical activity in area away from motor cortex) [26]. Therefore, clinical suspicion should be verified by conventional/aEEG recording according to availability. Accordingly, we applied aEEG on high risk infants for seizures or those with unclear clinical events. Interestingly, we found that the onset of 1st event was a statistically significant later in infants with Cz vs. those with Ez/ECz, we sought some of events might be missed in Cz group in particular the electrographic ones as aEEG was not applied for these infants impeding the early identification of abnormal brain activity. Matching with our concern, Wusthoff et al found seizures in HIE often lack distinct clinical signs and preemptive use of conventional EEG for seizures screening increases treatment success, as compared to confirmatory EEG after clinically-suspected seizures occur [27]. Moreover, an outstanding result was reported by Chalak et al [28] as they found frequency of Ez is increased during

rewarming period in cooled HIE infants and associated with death and disability. Ideally, treatment of Ez is time-critical, as infants treated within 1 hour of seizure onset had the lowest seizure burden and fewer seizures over the subsequent following 24 hours [29]. Therefore, particular attention should be paid for the role of EEG as a screening tool for high risk newborn and to be applied as early as possible to detect any electrographic events even before occurring clinically, bearing in mind the necessity of EEG monitoring during rewarming period.

In current study, 91% of newborn infants with seizures received ASMs. Our results were in close proximity to a study by Blume et al [30] in which 84 percent of infants with seizures were treated and increased up to 94 percent in NICU setting [31]. Also, we found that 46% of neonates with electrical seizures were refractory to the initial ASMs, in agreement with Glass study [32]. These data suggest that PB and phenytoin are incompletely effective for neonates with the most refractory seizures. Clinical trials are needed to determine which medication, or combination of medications, and which doses are most effective.

Previous studies have demonstrated that HIE, ischemic stroke, ICH, transient metabolic and electrolyte disturbances, systemic or CNS infections represented almost about 75% of causes leading to seizures in neonatal period [32-36]. In addition, Oh found that half of patients presented with two or more putative underlying etiologies [37]. Our cohort had good agreement with all of these studies as showed that the most common etiologies of seizure were HIE (53%), CNS infection (31%), ICH and stroke (26%) and about 38% of cases had more than one etiology. Indeed, identifying associations between seizure etiology and semiology might help in the segregation between acute symptomatic seizures and neonatal epilepsy. In current cohort, all subtle and myoclonic seizures were noticed in infants with HIE, while those with stroke and CNS infection developed focal/multifocal clonic seizures and those with metabolic/genetic causes developed tonic and tonic-clonic events. Our findings are not so far from previous studies as focal clonic seizures are strongly suggestive of acute symptomatic causes mainly stroke and infections [38, 39]. Therefore, Seizure semiology plays a vital role in identification of acute brain injury causes and may help in explicit prescription of treatment plan.

We sought to estimate the impact of neonatal seizures on subsequent neurological disorders such as death and developmental delays. Neonatal seizures are well-established cause of death; mortality rates have declined over time from 40% to (7- 16%) for term infants [40-42]. Our finding is not an exception as mortality rate was 29% in agreement with Al-Momen study [43]. In contrast, lower rates of death in term infants were reported in developed countries (13%-24%) [9, 10, 32, 40] and LMIC (22.5%) [37]. Mortality is still high in LMIC, so that it is vital to bear in mind the availability of prenatal care and advanced therapeutic intervention to preclude the undesirable outcome.

Of note, we used BSID-III in neurodevelopmental follow-up for both healthy infants and those developed neonatal seizures. We measured developmental outcomes of three main domains; cognitive, language and motor at 18 months of age and found a significant lower scores of all domains in infants developed seizures compared to healthy infants. Two different studies reported the neurodevelopmental outcome of infants with seizures in neonatal period using BSID scales; Ghosh [11] reported the outcome at 9-14 months for seizing and non-seizing infants with same brain insults in neonatal period and they found a significant lower cognitive and language domains in infants with seizures and Arican [12] reported the outcome at 18-24 months for infants received either PB or levetiracetam and they found lower means of cognitive, language and motor domains in PB group.

Inconsistent with current cohort, lower rates of developmental impairment in all tested domains were reported by Hunt [9]**;** cognitive 13 vs. 30%, language 45 vs. 50%, and motor 23 vs. 58.3% as they conducted follow-up study using BSID at age of 2 years for infants with Cz and Ez seizures in neonatal period. This could be explained by their larger sample size, different gestational age (near and full-term infants), different time of follow-up visits and different normed version of BSID; Australian population composite score means were used.

Importantly, our cohort spots important points such as low fifth minute Apgar scores, the requirement ASMs prior to discharge and the frequency of events as predictive risk factors for abnormal motor performance. Many studies also are in concordance with sensitivity of low Apgar score in prediction of abnormal outcome [19, 20, 22, 44-46]. Other contributing variables for adverse outcomes were also reported such as timing, frequency, duration of the seizures, and presence of status epilepticus [22, 23, 47-52]. Therefore, great attention should be paid from the 1st minute of life till time of discharge hoping to predict subsequent neurological impairment and to emphasize the importance early referral and intervention if needed.

In current cohort; survival distributions (time to death) were significant earlier in infants required initial resuscitation and advanced care (MV and HFOV), developed seizures within first 24 hours of life with special characteristics (as exceeding 6 days with flat or low voltage aEEG background, more than two AEDs were prescribed for optimum control and also were prescribed on their discharge plan) and also those exceeded 19 days admission in NICU. Moreover, survival outcome was ideal in cooled infant as none of them died prior end of study, though not reaching a significant level ($p=0.06$).

These findings are consistent with Glass study as they found that the death rate is doubled in non-responder neonates (seizures resistant to a loading dose of ASM) vs. the initial responders [32]. In addition, national institute of child health and human development (NICHD) trial found that severe HIE, AEDs and MV were independent predictors for death and disability at 18 month, whereas therapeutic hypothermia was a protective index against worse outcome [53].

Previous studies also demonstrated that mortality has an

excellent correlation with the etiology of seizures [32, 49, 54, 55]. While, the current study showed that HIE is associated with the highest mortality rate (39%) vs. other etiologies, although not reaching a significant level. ICH and CNS infection are also common causes of death in our study; each represents 33% of causes. Our results were in agreement with Glass study as they found the highest mortality was among neonates with HIE (26%) then those with ICH (13%) and ischemic stroke (4%) [32]. This may highlight important points as predictive risk factors for early death after neonatal seizures aiming to influence the direction ongoing care and expression of explicit clear decision to parents, yet the current study conducted on small number of infants.

The main strength of the current work is the assessment of 3 main developmental domains in both exposed and non-exposed infants to acute unfavorable brain events using Bayley-III. We have some limitation; we had to use the USA norms for the Bayley-III. Second, not all infants were monitored by aEEG and even those monitored by aEEG had no confirmatory raw EEG. Third, our cohort had small sample size due to high mortality rate. Lastly, we included infants with a variety of etiologies for neonatal seizures.

5. Conclusion

At last not least, occurrence of seizures in neonatal period may beget abnormal outcomes in the form of death and developmental disabilities. Having a child with a disability can put a lot of strain on a family, therefore, vigilance of neonatologist to certain factors in resuscitation room (APGAR score, need for resuscitation and gender), admission ward (onset of event, frequency of events, response of treatment), discharge summery (prescribed AEDs) are the stakeholders for prediction of mortality and future disability.

Abbreviations

AEDs: Antiepileptic drugs
aEEG: amplitude integrated electroencephalogram
ASMs: anti-seizure medications
BSID: Baylay scales of infant development
CNS: central nervous system
Cz: clinical seizures
ECz: electro-clinical seizures
Ez: electrical seizures
HFOV: high frequency oscillation ventilation
HIE: hypoxic ischemic encephalopathy
ICH: intracranial hemorrhage
MV: mechanical ventilation
PB: Phenobarbitone

Declaration

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Authors' Contributions

All authors contributed in the study design and data collection. All authors contributed in writing process of manuscript.

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