



Early predictors of remission in children and adolescents with new-onset epilepsy: A prospective study

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ABSTRACT

Purpose: This study aims to identify predictive factors of a two-year remission (2YR) in a cohort of children and adolescents with new-onset seizures based on baseline clinical characteristics, initial EEG and brain MRI findings. **Methods:** A prospective cohort of 688 patients with new onset seizures, initiated on treatment with antiseizure medication was evaluated. 2YR was defined as achieving at least two years of seizure freedom during the follow-up period. Multivariable analysis was performed and recursive partition analysis was utilized to develop a decision tree.

Results: The median age at seizure onset was 6.7 years, and the median follow-up was 7.4 years. 548 (79.7%) patients achieved a 2YR during the follow up period. Multivariable analysis found that presence and degree of intellectual and developmental delay (IDD), epileptogenic lesion on brain MRI and a higher number of pretreatment seizures were significantly associated with a lower probability of achieving a 2YR. Recursive partition analysis showed that the absence of IDD was the most important predictor of remission. An epileptogenic lesion was a significant predictor of non-remission only in patients without evidence of IDD, and a high number of pretreatment seizures was a predictive factor in children without IDD and in the absence of an epileptogenic lesion.

Conclusion: Our results indicate that it is possible to identify patients at risk of not achieving a 2YR based on variables obtained at the initial evaluation. This could allow for a timely selection of patients who require close follow-up, consideration for neurosurgical intervention, or investigational treatments trials.

1. Introduction

It is well established that despite the availability of numerous novel antiseizure medications (ASMs), one third of children with new-onset seizures will not achieve seizure remission [1–3]. These children endure the physical, psychological and social consequences of intractable seizures and face an elevated risk of death [4,5]. Despite its clinical

importance, the early prediction of treatment outcome remains a major challenge [6], with only a limited number of large, community-based, long-term studies evaluating early predictors of medical refractoriness in childhood epilepsy [7–9]. Certain childhood electroclinical syndromes, such as the self-limited focal epilepsy with centrotemporal spikes (SeLECTS) are known to have an excellent prognosis, while others, such as the Lennox-Gastaut syndrome, are associated with a

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much poorer outlook [10,11]. Although the determination of a specific electroclinical syndrome could provide guidance on management and clarify long-term prospects, syndromic diagnosis is frequently difficult to ascertain at the time of seizure onset [11]. An alternative approach is to develop a model that can predict treatment outcome based on variables obtained near the time of the initial evaluation. This would enable earlier consideration of surgical intervention or alternative non-medical treatments for children at high risk of not achieving seizure remission while avoiding the burden of ineffective polytherapy trials [12].

This prospective study aims to identify the prognostic variables for a two-year remission (2YR) following initiation of treatment with an ASM in children and adolescents with new-onset seizures, solely based on the clinical characteristics, EEG and brain MRI findings obtained at the time of the initial visit. A secondary objective is to calculate remission rates when stratified according to the latest International League Against Epilepsy (ILAE) classification of the epilepsies [11,13].

2. Materials and methods

2.1. Study design

A cohort of children and adolescents with new-onset seizures was identified from an ongoing centralized prospective study conducted at the American University of Beirut Medical Center (AUBMC) in association with the Lebanese Chapter of the International League against Epilepsy (ILAE). Although an official census is not available, it is estimated that the Lebanese population consists of 5.3 million individuals residing in the six governorates [14], with approximately 31% of the population being 17 years of age or younger [15]. This research study is a multi-center collaborative effort involving numerous neurologists distributed across the six governorates. These neurologists refer their patients with newly diagnosed seizures to the AUBMC, where a full clinical evaluation and extensive workup are performed.

As per protocol, the work-up included a detailed history and a thorough description of the events obtained from the patient and an eyewitness, complete physical and neurological examinations, a 3-hour sleep deprived video-EEG recording interpreted by experienced epileptologists, along with an epilepsy protocol brain MRI interpreted by a neuroradiologist with vast experience in the neuroimaging of patients with epilepsy. Patients were subsequently evaluated by telephone consultations and yearly follow-up visits with repeat EEGs as clinically indicated. More frequent follow-up visits were scheduled in case of seizure recurrence or adverse events related to ASM. At each follow-up visit or phone call, information about seizure frequency, changes in drug therapy or posology, adverse events and adherence to treatment were systematically recorded. Adherence to treatment was monitored through inquiries made to the caregiver/patient regarding the administration of ASM as prescribed. For children receiving valproate, carbamazepine, phenytoin or phenobarbital, routine monitoring of serum levels for these medications was conducted. However, due to the unavailability of local facilities for checking serum levels of newer ASMs and the high associated costs involved, which were not affordable for most patients or their parents, the serum levels of these drugs were rarely monitored.

2.2. Inclusion/exclusion criteria

For this study, we enrolled consecutive children ranging from 6 months to 18 years of age who presented with one or more unprovoked seizure between March 2010 and May 2016, and who were initiated on treatment with an ASM at the time of recruitment and had a follow-up of at least two years. Patients who presented with acute symptomatic or febrile seizures, as well as those with a history of functional seizures, alcohol or drug abuse, were excluded. Additionally, children with a follow-up period of less than two years while on ASM treatment and

those non-compliant to their prescribed treatment regimen, were excluded. Patients who died or underwent surgery after enrollment were censored at the time of death or surgery.

2.3. Ethical approval and patient consent

This study was approved by the Institutional Review Board of the AUBMC, and all patients enrolled in this study had an informed consent signed by one of their parents.

2.4. Brain MRI and classification of neuro-imaging findings

Brain MRIs were obtained from a 1.5 or 3T scanner (Ingenia; Phillips Healthcare) using an imaging-acquisition protocol that included 3D T1 (1 mm slice thickness) and 3D fast fluid-attenuated inversion recovery (FLAIR; 0.9- or 1-mm slice thickness) of the whole brain with multi-planar reconstruction, axial and coronal inversion recovery (2 mm slice thickness), axial T2 TSE and T2 FFE (4 mm slice thickness) and axial diffusion weighted images (4–5 mm slice thickness). The 3D images were obtained with no interslice gap.

MRI findings were classified as epileptogenic or non-epileptogenic based on previously published criteria [16–18]. MRI abnormalities consisting of isolated subcortical lesions or abnormal signal, nonspecific white matter hyperintensities, hydrocephalus, and brain atrophy were considered incidental findings.

2.5. Sleep deprived electroencephalogram (EEG) and classification of EEG findings

The EEGs were recorded on digital Nicolet machines (Natus^R Neurodiagnostics) with electrodes placed according to the International 10–20 system. At the initial visit, a 3-hour sleep deprived video-EEG with sleep recording was recorded from all patients. At each follow-up visit, a 60-minute sleep deprived EEG recording was performed. The EEG obtained at the initial visit were stratified according to the presence or absence of interictal epileptiform discharges (IEDs). Focal IEDs were classified based on their topography, morphology and presence or absence of focal slowing into focal maturational or focal non-maturational discharges [19]. The generalized spike wave discharges (GSWD) of the type seen in patients with a genetic generalized epilepsy (frequency of more than 2.5 Hz associated with a normal background) were labeled as idiopathic generalized discharges [19]. The GSWD of the type seen in patients with a developmental and epileptic encephalopathy (frequency of less than 2.5 Hz associated with a slow and disorganized background with or without concomitant focal or multifocal IEDs) were labeled as symptomatic generalized discharges.

2.6. Assessment of intellectual and developmental delay

All patients underwent an assessment to evaluate for the presence and severity of intellectual and developmental delay (IDD). Children younger than 6 years of age were evaluated using the Denver Development Screening Test [20]. Older children were assessed according to the Diagnostic and Statistical Manual of Mental Disorders criteria, which classifies intellectual delay as mild, moderate, severe, or profound based on deficits in intellectual functioning as well as difficulties in conceptual, social, and practical areas of living [21]. For example, children with mild intellectual delay may struggle with learning abilities and exhibit immaturity in social interactions, with communication and language skills that are more concrete than expected for their age. Children with moderate intellectual delay display marked limitations compared to their peers, with significant differences in social and communicative behavior. However, children with mild and moderate intellectual delay can still care for their personal needs, including eating, dressing and hygiene. Children with severe and profound intellectual delay have limited or very limited language development and have

substantial limitations in the conceptual domains. They require support or are completely dependent on others for all activities of daily living [21]. For the purpose of our analysis, we combined children with severe and profound delays into a single category, and included three groups of IDD (mild, moderate, or severe). To ensure the accuracy and consistency of the assessments, research fellows with specialized training in administering these tests were responsible for conducting the evaluation and scoring the degree of deficit. These chosen assessment tools were selected based on factors such as feasibility in terms of cost, accessibility, time requirements, and training considerations. Since our aim was to identify predictors of seizure remission based on baseline clinical variables, the IDD severity score determined during the initial visit was used for the analyses.

2.7. Seizure types and determination of the electroclinical syndrome

Seizure types were classified according to the latest ILAE 2017 classification of seizure types [22]. To ensure that the correct diagnosis of the epilepsy syndrome was made, the case report file of each child was entirely reviewed. The electroclinical syndromes were classified according to the latest International League Against Epilepsy (ILAE) classification of the epilepsies [11,13] with children stratified into one of five categories: [1] self-limited focal epilepsy, [2] genetic generalized epilepsy, [3] non-structural focal epilepsy, [4] structural focal epilepsy, [5] developmental and epileptic encephalopathy.

2.8. Outcome

A 2YR was defined as achieving at least two consecutive years of complete seizure freedom at any time during the entire follow-up period. Time to initial 2YR was defined as the elapsed time between treatment initiation and the time when a two-year seizure freedom was attained.

2.9. Variables

The following variables were collected for each patient at the time of enrollment in the study: [1] demographics; [2] disease characteristics (age at seizure onset, seizure types at onset, number of seizure types at onset, pretreatment number of seizures, time of seizure occurrence); [3] epilepsy risk factors (number of risk factors, family history of epilepsy, parental consanguinity, perinatal insult, febrile seizures, head trauma, CNS infection); [4] IDD (presence and severity); [5] IED types on initial EEG; [6] Brain MRI results (presence or absence of epileptogenic lesion).

2.10. Statistical analysis

Descriptive results were reported for the demographic and clinical characteristics. The cumulative time-dependent probability of 2YR was calculated using Kaplan-Meier survival tables and curves. Cox proportional hazards model was used to identify variables associated with 2YR. Assumptions of proportional hazards was tested using Log-Log. Variables yielding p -values < 0.2 in univariable analysis were tested in a multivariable analysis with significance level set at 0.05. Data were presented as hazard ratios (HR) and adjusted HR with 95% confidence intervals (CI).

In addition, a recursive partition analysis was performed to identify variables associated with higher or lower probabilities of achieving a 2YR. For this analysis, we used the Chi-square Automatic Interaction Detector with cross-validation. At each step, the Chi-square Automatic Interaction Detector algorithm chooses the independent variable that has the strongest interaction with the dependent variable using P values with a Bonferroni correction as splitting criteria. The final result is a decision tree with various nodes that can be used to predict the probability of achieving a 2YR in each subgroup. Statistical significance was set at the 5% level. All statistical analyses were performed using SPSS,

version 23.

3. Results

Of the 827 enrolled children, 139 were excluded for the following reasons: 72 were lost to follow-up or had a follow-up of less than two years and 67 were poorly compliant or received ASM for less than two years. This left 688 children who met the inclusion/exclusion criteria and who were included in the analyses (Fig. 1). The distribution of patients included in this study closely mirrored the geographical distribution of the population across Lebanon's six administrative governorates. Specifically, within our study cohort, 16% of the children resided in the Beirut governorate, 32% in Mount Lebanon, 23% in North Lebanon, 13% in the Bekaa, and 16% in South Lebanon and Nabatieh.

3.1. Demographic characteristics and epilepsy risk factors

The demographic characteristics and epilepsy risk factors of the study population are summarized in Table 1a. More than half of the children were males (59.2%) and 181 (26.3%) had IDD. The median age at time of seizure onset was 6.7 years (interquartile range (IQR) 2.3–11.0 years). The children were followed up for a mean duration of 7.2 years (range: 2.0–11.6 years; standard deviation: 2.3 years) and a median of 7.4 years (IQR 5.9–9.0 years). Risk factors for epilepsy were present in 459 children (66.7%) and included 208 children (30.2%) with a family history of epilepsy, 109 children (15.8%) born from consanguineous marriage, and 112 children (16.3%) with a history of perinatal insult.

3.2. Clinical characteristics

The clinical characteristics of the study population are summarized in Table 1b. The majority of patients (77.8%) experienced a single seizure type at the time of their initial evaluation. The most common seizure type was focal impaired awareness seizures (FIAS) which occurred in 267 children (38.8%). This was followed by focal to bilateral tonic-clonic seizures (FBTC) in 138 children (20.1%), focal aware seizures in 83 children (12.1%) and generalized onset tonic-clonic seizures (GOTC) in 72 children (10.5%). Prior to treatment initiation, 350 children (50.9%) experienced between one and five seizures, while 233 children (33.9%) experienced more than 100 seizures. This typically was the case in children who experienced frequent daily absence seizures ($n = 82$), myoclonic seizures ($n = 55$), or epileptic spasms ($n = 67$). A small percentage (19.2%) experienced both nocturnal and diurnal seizures. IEDs were observed on the initial EEG of 487 children (70.8%). GSWD of the idiopathic type and focal non-maturational discharges occurred more frequently (23.8% and 24.0% respectively) than GSWD of the symptomatic type and focal maturational discharges (12.4% and 12.1% respectively). An epileptogenic lesion was present on the brain MRI of 191 (27.8%) children, with MCD identified in 61 (31.9%) and hypoxic injury in 46 (24.1%). Out of the 191 patients with epileptogenic lesions detected on brain MRI, 140 exhibited epileptiform discharges that lateralized to the side of the lesions. Among the remaining 51 patients, 35 displayed no interictal discharges on EEG, and 16 patients exhibited discordant or multifocal epileptiform discharges. In cases where no associated epileptiform discharges were present, the brain lesion was considered likely epileptogenic, as the seizure semiology was concordant with the location of the brain lesion. Of the 10 patients with discordant epileptiform discharges, 6 showed hypersarrhythmia on their EEG recordings.

3.3. Treatment characteristics

During the follow-up period, 322 children (46.8%) were prescribed only one ASM, while 187 children (27.2%) received two ASMs, either as monotherapy or in combination. The number of ASMs prescribed ranged from 1 to 10 with a median of two drugs. The patients were treated with

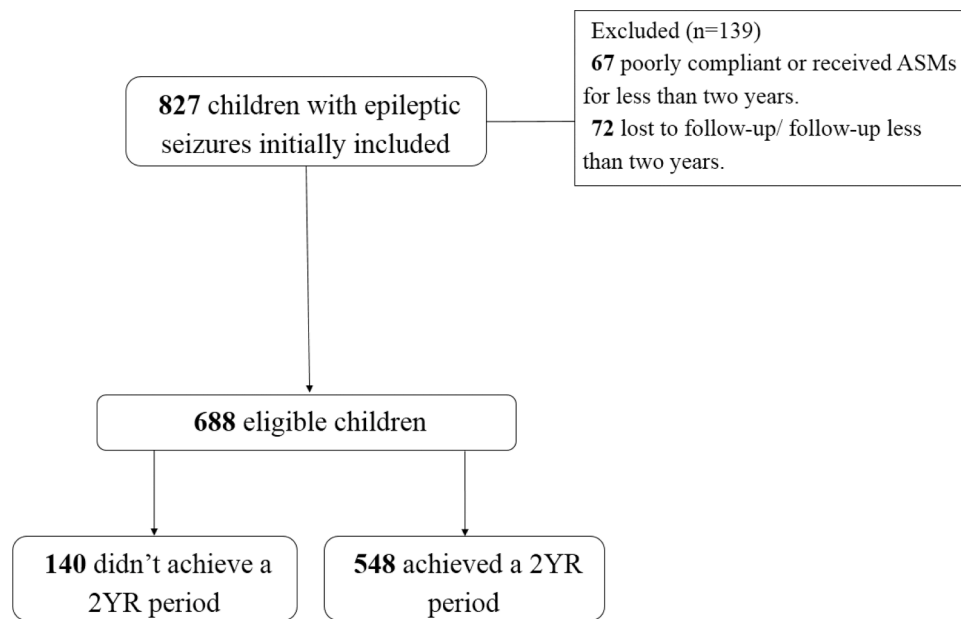


Fig. 1. Flow chart of the study cohort. 2YR: 2-year remission, ASMs: antiseizure medications.

Table 1a
Demographic characteristics and epilepsy risk factors of the study population.

Variable	Mean (STD)	Range	Median (IQR)
Age at seizure onset (years)	7.0 ± 5.0	0.5–17.6	6.7 (2.3–11.0)
Duration of follow-up (years)	7.2 ± 2.3	2.0–11.6	7.4 (5.9–9.0)
Variable			
Gender			
Male	407 (59.2)		
Female	281 (40.8)		
Age at seizure onset			
0.5 <2 yrs	157 (22.8)		
2-<5 yrs	116 (16.9)		
5-<12 yrs	272 (39.5)		
12-<18 yrs	143 (20.8)		
Intellectual and developmental delay			
None	507 (73.7)		
Mild	58 (8.4)		
Moderate	52 (7.6)		
Severe	71 (10.3)		
Presence of epilepsy risk factors			
Yes	459 (66.7)		
Number of epilepsy risk factors			
None	229 (33.3)		
1	266 (38.7)		
2	159 (23.1)		
≥3	34 (4.9)		
Type of epilepsy risk factor			
Family history of epilepsy	208 (30.2)		
Consanguinity	109 (15.8)		
Perinatal insult	112 (16.3)		
Febrile seizures	85 (12.4)		
Head trauma	36 (5.2)		
CNS infection	15 (2.2)		

STD: standard deviation; IQR: interquartile range; CNS: central nervous system.

an ASM for a mean duration of 4.0 ± 1.8 years (range: 2.0–10.5 years). The most frequently prescribed ASM was valproate (73.4%), followed by levetiracetam (32.1%). Nonpharmacological treatments were received by 51 children (7.4%), that included 23 who underwent epilepsy surgery, 29 inserted with a vagus nerve stimulator, and two treated with the ketogenic diet.

3.4. Remission rates

To date, 548 children (79.7%) have achieved a 2YR. The median time to achieve a 2YR was 2.1 years (95% CI: 2.0–2.1), with a range of 2.0 to 9.7 years. The cumulative probabilities of achieving a 2YR were 43.1% (95% CI: 39.4–46.8%) at 24 months, 69.3% (95% CI: 65.9–72.9%) at 36 months, 75.5% (95% CI: 72.1–78.8%) at 48 months, 81.7% (95% CI: 78.6–84.8%) at 72 months, and 86.6% (95% CI: 83.3–90.0%) at 120 months after treatment initiation (Fig. 2). At last follow-up, 502 (73.0%) of the 688 children included in our study experienced a terminal two-year remission.

3.5. Determinants of remission

3.5.1. Univariable analysis

Univariable analysis showed that several factors were associated with a lower probability of remission. These included a younger age at seizure onset, a greater number of pretreatment seizures, experiencing three or more types of seizures at onset, the presence and degree of IDD, the presence of an epileptogenic lesion on MRI, mixed time of seizure occurrence (both nocturnal and diurnal), a history of perinatal insult, parental consanguinity, and the presence of focal non-maturation or generalized discharges of the symptomatic type (Table 2).

3.5.2. Multivariable analysis

In multivariable analysis (Table 2), factors that independently predicted a lower probability of remission were a greater number of seizures prior to treatment initiation, the presence and severity of IDD and the presence of an epileptogenic lesion on MRI.

Children who experienced more than 100 seizures prior to treatment initiation with an ASM had a lower probability of achieving a 2YR compared to those who experienced up to five seizures (HR= 0.7, 95% CI: 0.5–0.9, *p* = 0.011). This probability was further reduced for children with a history of 11–100 seizures prior to treatment (HR= 0.6, 95% CI 0.4–0.8, *p* = 0.002). The probability of achieving a 2YR varied depending on the presence and severity of IDD. While no significant difference was found between children with mild or moderate IDD and those with no IDD, the probability of achieving a 2YR was significantly lower in children with severe IDD (HR= 0.4, 95% CI 0.2–0.6, *p* < 0.001) (Supplementary Figure 1). Finally, the presence of an epileptogenic lesion on brain MRI significantly reduced the probability of achieving a

Table 1b
Clinical characteristics of the study population.

Seizure types at presentation^a	
Focal onset	
Focal impaired awareness seizures	267 (38.8)
Focal aware seizures	83 (12.1)
Focal to bilateral tonic-clonic seizures	138 (20.1)
Generalized onset seizures	
Generalized onset tonic-clonic seizures ^b	72 (10.5)
Absence seizures	82 (11.9)
Myoclonic jerks	55 (8.0)
Epileptic Spasms	67 (9.7)
Other ^c	32 (4.7)
Unknown onset	
Unknown-onset tonic clonic seizures	69 (10.0)
Pretreatment number of seizures	
1–5	350 (50.9)
6–10	42 (6.1)
11–100	63 (9.2)
>100	233 (33.9)
Number of seizure types at presentation	
1	535 (77.8)
2	127 (18.5)
≥3	26 (3.8)
Time of seizure occurrence	
Nocturnal	162 (23.5)
Diurnal	394 (57.3)
Mixed	132 (19.2)
IED on EEG	
No	201 (29.2)
Yes	487 (70.8)
IED type on EEG	
Focal	
Maturation	83 (12.1)
Non-maturation ^d	165 (24.0)
Generalized	
Idiopathic ^d	164 (23.8)
Symptomatic	85 (12.4)
Epileptogenic lesion on MRI*	
Yes	191 (27.8)
No	489 (71.1)
Type of Epileptogenic lesion	
Malformations of cortical development	61 (31.9)
Periventricular leukomalacia/hypoxia	46 (24.1)
Vascular	31 (16.2)
Mesial temporal sclerosis	15 (7.9)
Neurocutaneous syndromes	13 (6.8)
Other ^e	25 (13.1)

IED: interictal epileptiform discharges; EEG: electroencephalogram; MRI: magnetic resonance imaging.

^a Total percentage above 100% because some children experienced more than one seizure type at presentation.

^b Generalized tonic-clonic seizures were considered of generalized onset if the child had definite absence seizures or myoclonus, or if the event was witnessed from onset with no signs of focality.

^c Other seizure types include tonic seizures in 13 children (1.9%), eyelid myoclonia in 9 children (1.3%), drop attacks in 8 children (1.2%) and myoclonic absence and myoclonic-ataxic seizures in one child each (0.1%).

^d 10 children were diagnosed with photosensitive occipital lobe epilepsy and had both focal and idiopathic generalized epileptiform discharges.

* A brain MRI was not performed on 8 children.

^e Other lesions consisted of post-infectious encephalomalacia with cortical gliosis in 7 (3.7%), metabolic disorders and post-traumatic encephalomalacia and gliosis in 5 children each (2.6%), tumors in 5 children (2.2%) and leukodystrophy in 3 (1.5%).

2YR (HR=0.6, 95% CI 0.5–0.8, $p < 0.001$) (Supplementary Figure 2).

3.5.3. Recursive partition analysis

The recursive analysis identified those same variables that partitioned the patients into a decision tree with five groups (Fig. 3). The first important predictor of failure to achieve remission was the presence and severity of IDD, which classified children into three groups: those with no IDD, those with mild or moderate IDD and those with severe IDD.

60% of children with severe IDD and 31.5% of children with mild or moderate IDD failed to achieve a 2YR compared to 10.6% of children with no IDD.

The next predictor variable, the presence or absence of an epileptogenic lesion on brain MRI, only applied to children with no IDD where 29.1% of children with a lesion failed to achieve a 2YR compared to 7.1% of children with no lesion. Finally, the terminal predictor in children with no IDD and no epileptogenic lesion was the number of seizures prior to treatment initiation; 13.7% of children with more than 10 seizures prior to treatment initiation failed to achieve remission, compared to 3.4% in children with a lower number of seizures.

3.6. Remission rates stratified according to epilepsy syndromes

The majority of children in the study were diagnosed with focal epilepsy, with 121 children (17.6%) diagnosed with a self-limited focal epilepsy (SeLFE), 132 (19.2%) with a structural focal epilepsy and 186 (27.0%) with a non-structural focal epilepsy. 155 (22.5%) children were diagnosed with a genetic generalized epilepsy (GGE), while 94 (13.7%) were diagnosed with a developmental and epileptic encephalopathy (DEE). The associated 2YR rates for each syndrome are shown in Fig. 4. The groups of children most likely to achieve a 2YR were those diagnosed with a SeLFE (97.5%), GGE (92.9%) and non-structural focal epilepsies (87.1%). In contrast, there was a lower likelihood of achieving a 2YR in children diagnosed with a structural focal epilepsy (59.8%) or DEE (47.9%). It is worth noting the variable distribution of epilepsy syndromes across different age groups. The highest prevalence of DEE was observed in children with seizure onset between 0 and 2 years (44.6%), while the lowest between 12 and 18 years (0.7%). Conversely, the lowest prevalence of GGE was in children with seizure onset between 0 and 2 years (4.5%), while the highest was in children with onset between 12 and 18 years (42.0%) (Supplementary Figure 3).

4. Discussion

Our results indicate that 79.7% of children with new-onset seizures will achieve a 2YR after treatment initiation. The independent negative predictors of a 2YR include the presence and severity of IDD, the presence of an epileptogenic lesion on brain MRI and the number of pre-treatment seizures. These results suggest that it is possible to identify children who are at risk of not achieving a 2YR based on variables obtained at the time of initial evaluation.

The percentage of children who achieved a 2YR in our study is comparable to the 74% rate reported in a previous study of 594 children with newly diagnosed epilepsy [23]. The slightly lower remission rate in the previous study is likely due to a shorter follow-up period (median of 5.3 years compared to 7.4 years in our study) and a younger age at seizure onset (median of 5.3 years compared to 6.7 years in our study). Both studies, however, are consistent in showing that most children with new-onset seizures will reach a 2YR at some point during their clinical course, with most remissions occurring in the early years following treatment initiation.

Our data ascertaining that the presence and severity of IDD is one of the key factors impacting the likelihood of achieving a 2YR is consistent with the findings of previous studies [24–26]. This is however the first study to clearly indicate that the presence and severity of IDD are the most significant baseline variables that influence the probability of attaining a 2YR. This conclusion was supported by the adjusted hazard ratio and the principal predictor variable of the recursive analysis, which showed that children with normal development had the highest likelihood of achieving a 2YR, those with mild to moderate IDD had a lower probability, and those with severe IDD had the lowest odds.

In this study, 27.8% of children were found to have an epileptogenic lesion on their brain MRI. Previous studies reported etiologically related neuroimaging abnormalities in 13%–18% of children with new-onset seizures [27–29]. The higher percentage in our study is likely due to

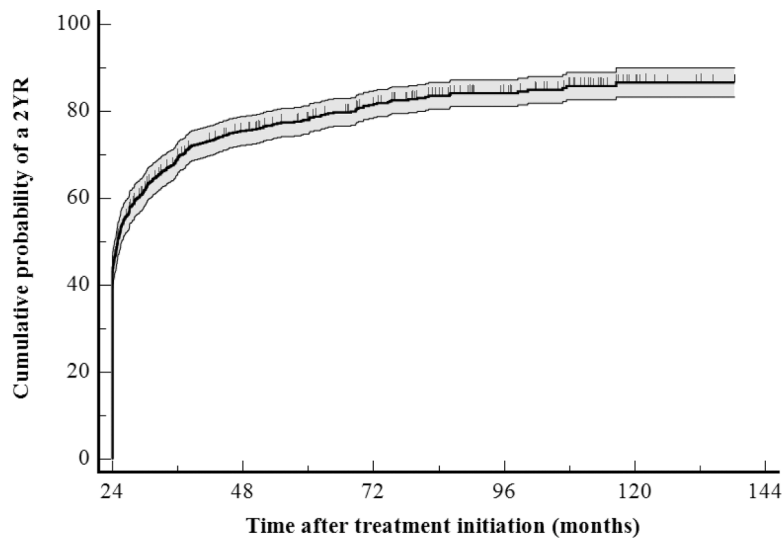


Fig. 2. Kaplan-Meier Curve: Cumulative probability of achieving a two-year remission (2YR) following treatment initiation. Dashed lines represent censored data. Gray shade represents 95% confidence interval.

Table 2

Univariable and multivariable Cox regression results for two-year remission by clinical characteristics, EEG and brain MRI obtained at the initial visit.

Comparison	Unadjusted HR			Adjusted HR		
	HR	95%CI	p-value	HR	95%CI	p-value
Pretreatment number of seizures						
1-5	1		–	1		–
6-10	0.92	0.65–1.29	0.612	0.82	0.57–1.18	0.284
11-100	0.53	0.38–0.74	<0.001	0.58	0.41–0.82	0.002
>100	0.63	0.52–0.77	<0.001	0.70	0.53–0.92	0.011
Intellectual and developmental delay						
None	1		–	1		–
Mild	0.65	0.48–0.89	0.007	0.79	0.56–1.12	0.181
Moderate	0.49	0.34–0.71	<0.001	0.68	0.44–1.03	0.072
Severe	0.25	0.17–0.37	<0.001	0.35	0.21–0.59	<0.001
Presence of epileptogenic lesion on MRI	0.47	0.38–0.58	<0.001	0.64	0.49–0.82	<0.001
Female vs. male	0.98	0.82–1.16	0.769			
Age at seizure onset						
0.5-<2 yrs	1		–	1		–
2-<5 yrs	1.44	1.08–1.91	0.012	0.95	0.69–1.30	0.759
5-<12 yrs	1.7	1.34–2.16	<0.001	1	0.76–1.35	0.903
12-<18 yrs	2.03	1.56–2.65	<0.001	1	0.73–1.38	0.962
Number of seizure types at onset						
1	1		–	1		–
2	0.91	0.73–1.13	0.385	1.01	0.8–1.27	0.986
≥3	0.41	0.23–0.7	0.001	0.56	0.3–1.03	0.062
Time of seizure occurrence						
Nocturnal	1		–			–
Diurnal	1.05	0.86–1.28	0.645	1.16	0.93–1.4	0.188
Mixed	0.67	0.51–0.87	0.003	0.96	0.71–1.31	0.830
Presence of epilepsy risk factors	0.91	0.76–1.08	0.304			
Number of epilepsy risk factors						
None	1		–	1		–
1	1		–	1.1	0.87–1.36	0.414
2	0.82	0.66–1.03	0.093	0.99	0.7–1.39	0.950
≥3	0.72	0.47–1.11	0.136	0.99	0.55–1.80	0.991
Perinatal insult	0.67	0.52–0.86	0.002	1.04	0.76–1.43	0.794
Febrile seizure	1.19	0.94–1.52	0.153	1.26	0.93–1.72	0.135
Head trauma	1.15	0.81–1.65	0.434			
CNS infection	0.7	0.37–1.31	0.26			
Parental consanguinity	0.73	0.6–0.9	0.003	0.85	0.64–1.12	0.241
Family history of epilepsy	1.05	0.89–1.24	0.579			
IED type on initial EEG						
No discharges	1		–	1		–
Focal maturational	1.23	0.95–1.61	0.118	1.05	0.78–1.42	0.747
Focal non-maturational	0.69	0.54–0.88	0.002	0.82	0.63–1.06	0.135
Generalized idiopathic	1.19	0.96–1.5	0.12	1.14	0.85–1.53	0.363
Generalized symptomatic	0.37	0.26–0.52	<0.001	1.09	0.66–1.77	0.742

Abbreviations: CI; confidence interval; HR: hazard ratio; CNS: central nervous system; IED: interictal epileptiform discharges; EEG: electroencephalogram; MRI: magnetic resonance imaging.

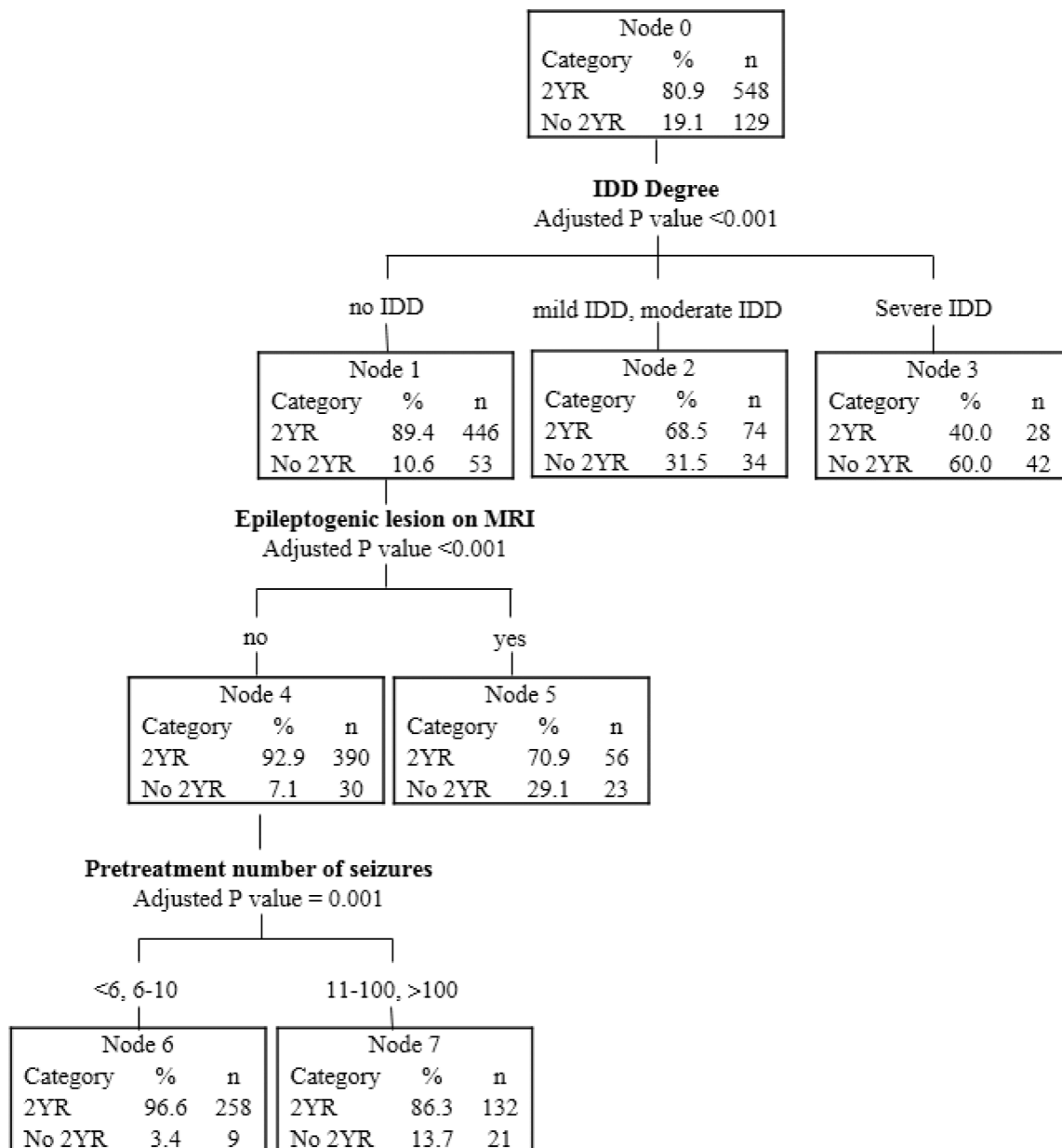


Fig. 3. Recursive partition analysis stratified children into a decision tree with 5 groups based only on the presence and severity of IDD, presence of epileptogenic lesion on MRI, and pretreatment number of seizures. IDD: intellectual and developmental delay, MRI: magnetic resonance imaging, 2YR: two-year remission.

obtaining a dedicated epilepsy protocol MRI on all children, whereas prior studies evaluated children with brain CT and non-epilepsy protocol MRI [27,28,30] or excluded children with IDD [29]. Those results emphasize the importance of obtaining an epilepsy protocol brain MRI as the presence of an epileptogenic lesion was a significant negative predictor for achieving a 2YR. Most studies evaluating the prognosis of childhood epilepsy have reported that a remote symptomatic etiology was predictive of poor seizure outcome [7,8,23,31,32]. However, in our study, the recursive partitioning analysis found that this variable was only significant in children without evidence of IDD, indicating that the presence of IDD supersedes the detection of an epileptogenic lesion as a determinant of achieving a 2 YR. Although the relationship between the nature of the pathologic substrate and medical refractoriness has been studied in adults [33–35], such analysis was beyond the scope of this study and will be the subject of future research.

Our findings are also consistent with other studies [8,9,36–39] that have shown that a higher number of pretreatment seizures is associated

with a significantly lower probability of attaining a 2YR. However, the recursive partitioning analysis in our study found that this factor was only significant in children without IDD and without a lesion on brain MRI. Actually, nearly all children in this study with more than 100 seizures prior to treatment initiation experienced absence seizures, myoclonic seizures or epileptic spasms. Additionally, a subgroup analysis in our study revealed that the association between the number of pretreatment seizures and the likelihood of achieving a 2YR was only significant for children with focal-onset seizures. This finding is concordant with other observational studies [40,41], that when critically reviewed [42], documented that the relationship between high initial seizure frequency and poor outcome was only true for children experiencing focal impaired awareness seizures. Our data therefore support the conclusion that the type of epilepsy rather than the number of pretreatment seizures is the major variable that impacts outcome [42].

In our univariable analysis, we found that seizure onset within the

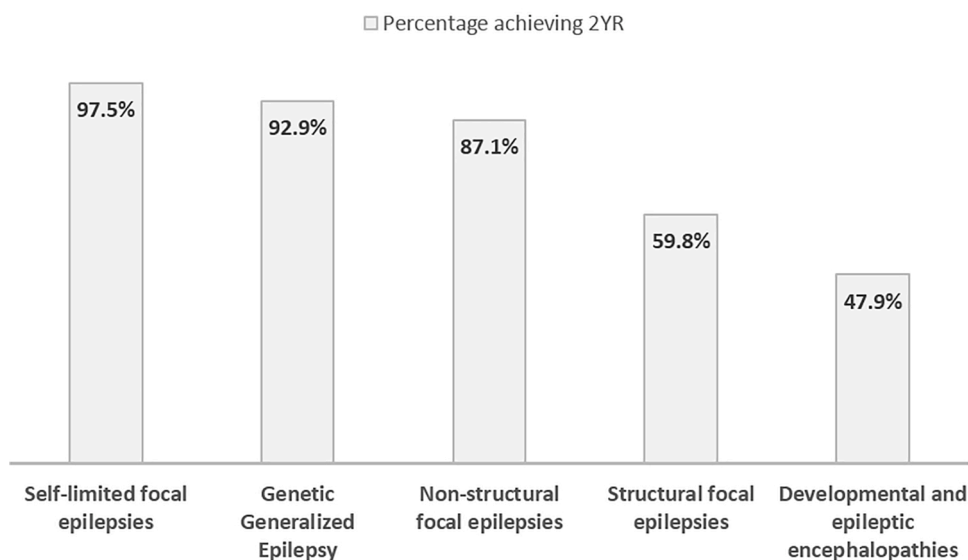


Fig. 4. Percentages of children achieving a two-year remission (2YR) stratified according to the epilepsy syndromes.

first two years of life was associated with a significantly lower probability of achieving a 2YR, a result in line with previous studies [8,43,44]. Nevertheless, in a multivariable analysis, we and others [9] found that there was no independent association between these variables. The divergent outcomes across different age groups are therefore more likely attributable to the prevalence of specific epilepsy syndromes in various age ranges. For instance, in our study, DEE was the most common diagnosis in children with seizure onset in the first two years of life, whereas GGE was the most prevalent among those with onset between 12 and 18 years.

Previous studies that evaluated the prognostic value of IED have yielded conflicting results. While some investigators found no significant association between prognosis and the presence of IED [8,23,26], others indicated that their presence was associated with a poorer outcome [43]. Those studies however only assessed for the presence or absence of any type of IED [8,23,26] or at best categorized them into focal or generalized discharges [43]. In our study, we divided the IED into four types and found that symptomatic generalized discharges and focal non-maturational discharges were associated with a significantly lower likelihood of attaining a 2YR in the univariable analysis. This association was however not significant in the multivariable analysis with the recursive partitioning analysis indicating that the coexistence of IDD in the case of symptomatic generalized discharges and epileptogenic lesions in the case of focal non-maturational discharges overshadowed the importance of those types of IEDs as significant negative predictor variables.

Our study has several strengths that make its findings robust and reliable. Those include its prospective design and the inclusion of a large number of consecutive children referred from all governorates of the country, which enhances the generalizability of the results. Additionally, the study evaluated many variables that might impact prognosis and included a long-term follow-up, which allowed for a comprehensive evaluation of the outcomes. Furthermore, the seizures and epilepsies were classified according to the ILAE guidelines, providing a standardized and reliable classification system. Finally, this study not only confirmed the negative association between certain variables and the probability of a 2YR but is the first to perform a recursive analysis that allowed for a prioritization and splitting of those independent factors. Our study has also several limitations that need to be acknowledged. Firstly, the duration of follow-up was variable, which might have influenced the results. Secondly, infants below the age of 6 months at the time of their initial presentation were not included according to the study protocol. Due to the higher prevalence of drug-resistant epilepsy

in this age group, this exclusion might have impacted the results by potentially overestimating the remission rates. Another limitation is that some children were evaluated with a 1.5 Tesla MRI, which might have led to an underestimation of epileptogenic lesions. Furthermore, the serum levels of the newer ASMs were not routinely checked, and we relied on the information provided by caregivers or the parents regarding treatment adherence for these particular ASMs. In addition, in children younger than 6 years of age, we relied on the Denver Development Screening Test to assess for the presence and severity of IDD without confirmation from another assessment tool. Finally, genetic testing was not systematically obtained, especially in children with a DEE, which might have impacted the results. Future studies should aim to validate and expand upon the predictive variables identified in our investigation and to assess their generalizability to diverse populations.

5. Conclusions

This study provides valuable insights into the prognosis of children with new-onset seizures. The results indicate that the likelihood of achieving a 2YR can be assessed at the time of the initial evaluation, providing additional perspectives for counseling patients and their parents. The findings will allow for a timely selection of children who might require close follow-up or early neurosurgical intervention, or for management with investigational treatments.

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Data availability

Data available on request from the corresponding author.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in

the online version, at doi:10.1016/j.seizure.2023.06.007.

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