Factor Associated With The Outcomes of Children with Epilepsy At Abdul Moeloek Hospital In Lampung Province, Indonesia

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Abstract *:* Epilepsy is a condition that describes recurrent seizure episodes more than 24 hours apart that occur without provocation. Epileptic seizures are clinical manifestations that are caused by the abnormal and excessive electrical activity of the brain from a group of neurons. Epilepsy outcome is controlled seizures or uncontrolled seizures. Uncontrolled epilepsy is epilepsy that still occurs after 6 months of therapy. There are several factors that influence the outcome of epilepsy in children include age at onset first seizures, initial seizure frequency, type of seizure, developmental delay, first electroencephalography, antiepileptic drug therapy and neurological deficits. This study aims to determine the factors associated with the outcome of children with epilepsy at Abdul Moeloek Hospital Lampung Province, Indonesia. This research use observational analysis method with cross sectional design. Collecting data using medical records. Bivariate analysis and multivariate analysis using logistic regression test. In total of 75 children who are being analysed in seven factors, bivariate test showed that the initial seizure frequency factor (p = 0.000), types of seizures (p = 0.03), antiepileptic drug therapy (p = 0.014) and multivariate analysis of test results that the initial seizure frequency factor (OR = 14,500).outcome of children with epilepsy at Abdul Moeloek Hospital Lampung Province, Indonesia.

Keywords *:* Child Epilepsy, Epilepsy Outcomes, Risk Factors.

INTRODUCTION

Epilepsy is defined as a brain disorder that is characterized by at least two unprovoked muscle spasms more than 24 hours [1]. Spasm episodes are caused by the unstable brain electricity which further disrupt muscle coordination and clinical manifested on muscle stiffness or muscle repetitive jolts [2].

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Epileptic sufferers in South East nations, the prevalence that is found in Thailand is 7,2 per 1.000 school kids, meanwhile in Singapore the prevalence is 3,5 per 1.000 school kids [3]. The number of epilepsy cases in Indonesia is 700.000-1.400.000 cases with the increasement of 70.000 new cases every year and is estimated that around 40-50% of those prevalence occur in children [4].

Controlled epilepsy is an epilepsy that has been seizure-free for at least 6 months [5]. Uncontrolled epilepsy is a chronic disorder that is not merely characterized by repetitive seizure, but has various medical and psychosocial implications. Children with uncontrolled epilepsy have a high risk of developmental delays, physical accidents, learning problem, cognitive delays, social problems, difficulty being independent and being a burden for the family and environment [6].

Nowadays, analyzing special aspects of epilepsy, including the risk of medical failures and the risk of repetitive epileptic remission is being considered. Various types of seizure happen in children, and the diagnosis depends on the type and causes. The disease's course varies from early remission after the first drug use initiations to permanent and uncontrolled seizure with multiple drug failures. The recovery from seizure happens more frequently in children than in adults, despite of using various types of medicines, the first period of treatment fails in many cases and not all children with seizure can be cured. Six to forty-one percent children with seizure do not respond to medical treatments because of the uncontrolled epilepsyi [7].

Several studies have been conducted to look for the factors that are related to epilepsy outcomes. Studies conducted on children states several factors associated with epilepsy outcomes including age of seizure onset, initial seizure frequency, types of seizure, developmental delays, initial electroencephalography features, antileptic drug therapy, and neurological deficits.

The study about factors associated with epilepsy outcomes, controlled or uncontrolled epilepsy in children has not been performed much in Lampung. Based on the background above, the author is interested in researching the factors that influence whether epilepsy is controlled or uncontrolled in children at Abdul Moeloek Hospital Lampung Province, Indonesia..

SUBJECT AND METHOD

This study used an observational analytical method with cross sectional approach. This study was conducted at Abdul Moeloek Hospital in Lampung Province, Indonesia on November 2020.

The study sampling technique used consecutive sampling, the number of sampling was 75 people. The population of the study were pediatric patients aged less than 18 years old who were diagnosed with epilepsy at Abdul

Moeloek Hospital in Lampung Province, Indonesia. The inclusion criteria for this study ere children aged less than 18 years old who were diagnosed with epilepsy at Abdul Moeloek Hospital in Lampung Province, Indonesia from January 2019 to November 2020 period. The exclusion criteria for this study were children with routinely controlled epilepsy and children with epilepsy who had incomplete medical record data.

The independent variables in this study were age of seizure onset, initial seizure frequency, types of seizure, gross motor skills, initial electroencephalography features, antiepileptic drug therapy, and neurological deficits. The dependent variables in this study were the epilepsy outcomes in children.

The instruments used in this study were data recording sheets, stationeries, and medical records. The data collection methos used secondary data in the form of children epilepsy's medical records Abdul Moeloek Hospital in Lampung Province, Indonesia from January 2019 to November 2020 period. Then the data was analyzed using univariate analysis, bivariate analysis with Chi Square test and multivariate analysis using the logistic regression test with Backward method.

RESULTS

After taking secondary data from the data records of 75 children with epilepsy, then the data will be proceeded with univariate, bivariate, and multivariate analysis of the research data.

Table 1. Frequency Distribution of Children with Epilepsy

Characteristic	Frequency	Percentage (%)
Age of seizure onset		
>1 year	57	76
≤1 year	18	24
Initial Seizure Frequency		
≤5 times/day	43	57,3
>5 times/day	32	42,7
Type of Seizure		
Focal	36	48
Common	39	52
Developmental Delay		
There isn't any	63	84
There is	12	16
Initial EEG Features		
Normal	6	8
Abnormal	69	92
OAE Therapy		
1 OAE	54	72

≥2 OAE	21	38
Neurological Deficits		
There isn't any	60	80
There is	15	20
Total	75	100

Table 1 shows the characteristic of children with epilepsy. Most of the children who suffer from epilepsy at Abdul Moeloek Hospital Lampung Province, Indonesia. is a child who has an age of seizure onset >1 year (76%), initial seizure frequency <5 times/day (57,3%), common type of seizure (52%), child with no developmental delays (84%), abnormal initial electroencephalography features (92%), using antiepileptic drug monotherapy/ 1 OAE (72%), and child with no neurological deficits (80%).

Then proceeding with bivariate analysis which aims to determine the factors associated with epilepsy outcomes at Abdul Moeloek Hospital Lampung Province, Indonesia. with the results of Chi-square test, as follows:

Table 2. Correlation Between The Age of Seizure Onset and Epilepsy Outcomes at Abdul Moeloek Hospital Lampung Province, Indonesia.

Age of Seizure Onset	Epilepsy Outcome				P
	Controlled		Un-controlled		
	n	%	n	%	
> 1 year	27	81,8	30	71,4	
≤1 year	6	18,2	12	28,6	0,439
Total	33	100%	42	100%	

Table 2 The results of the study show that from 57 children with the age of seizure onset of >1 year, 27 children (81,8%) have controlled epilepsy and 30 children (71,4%) have uncontrolled epilepsy, meanwhile from 18 children with the age of seizure onset of <1 year, 6 children (18,2%) have controlled epilepsy and 12 children (28,6%) have uncontrolled epilepsy. The Chi Square test results show a p-value of 0,439 (p>0,05). Based on those data, it can be concluded there is no correlation between the age of seizure onset and the epilepsy outcomes in children with epilepsy at Abdul Moeloek Hospital Lampung Province, Indonesia..

Table 3. Correlation Between Initial Seizure Frequency and Epilepsy Outcomes at Abdul Moeloek Hospital Lampung Province, Indonesia.

Initial Seizure Frequency	Epilepsy Outcome				P
	Controlledd		Un-controlled		
	n	%	n	%	
≤5 times/day	29	87,9	14	33,3	0,000
>5 times/day	4	12,1	28	66,7	
Total	33	100%	42	100%	

Table 3 shows that from 43 children who have initial seizure frequency <5 times/day, 29 children (87,9%) have controlled epilepsy and 14 children (33,3%) have uncontrolled epilepsy, meanwhile from 32 children who have initial seizure frequency >5 times/day, 4 children (12,1%) have controlled epilepsy and 28 children (66,7%) have uncontrolled epilepsy. The result of Chi Square test is p-value 0,000 (p<0,05). Based on those data, it can be concluded that there is a correlation between initial seizure frequency and the epilepsy outcomes in children with epilepsy at Abdul Moeloek Hospital Lampung Province, Indonesia.

Table 4. Correlation Between The Seizure Types and Epilepsy Outcomes at Abdul Moeloek Hospital Lampung Province, Indonesia.

Seizure Types	Epilepsy Outcome				P
	Controlled		Un-controlled		
	n	%	n	%	
Focal	21	63,6	15	35,7	0,03
Common	12	36,4	27	64,3	
Total	33	100%	42	100%	

Table 4 shows from 36 children with focal seizure type, 21 children (63,6%) have controlled epilepsy and 15 children (35,7%) have uncontrolled epilepsy, meanwhile from 39 children with common seizure type, 12 children (36,4%) have controlled epilepsy and 27 children (64,3%) have uncontrolled epilepsy. The result of Chi Square test is p-value 0,03 (p<0,05). Based on those data, it can be concluded that there is a correlation between the type of seizure and epilepsy outcomes in children with epilepsy at Abdul Moeloek Hospital Lampung Province, Indonesia.

Table 5. Correlation Between Developmental Delay and Epilepsy Outcomes at Abdul Moeloek Hospital Lampung Province, Indonesia.

Developmental Delay	Epilepsy Outcome				P
	Controlled		Un-controlled		
	n	%	n	%	
There isn't	29	87,9	34	81	0,621
There is	4	12,1	8	19	
Total	33	100%	42	100%	

Table 5 shows from 63 children with no developmental delay, 29 children (87,9%) has controlled epilepsy and 34 children (81%) have uncontrolled epilepsy, meanwhile from 12 children with developmental delay, 4 children (12,1%) have controlled epilepsy and 8 children (19%) have uncontrolled epilepsy. The result of Chi Square test is p-value 0,621 (p>0,05). Based on those data, in can be concluded that there is no correlation between

developmental delays and epilepsy outcomes in children with epilepsy at Abdul Moeloek Hospital Lampung Province, Indonesia.

Table 6. Correlation Between Initial Antiepileptic Drug Therapy and Epilepsy Outcomes at Abdul Moeloek Hospital Lampung Province, Indonesia.

Initial EEG Features	Epilepsy Outcome				P
	Controlled		Un-controlled		
	n	%	n	%	
Abnormal	3	9,1	3	7,1	1,000
Normal	30	90,9	39	92,9	
Total	33	100%	42	100%	

Table 6 shows from 6 children with normal initial electroencephalography features (EEG), 3 children (9,1%) have controlled epilepsy and 3 children (7,1%) have uncontrolled epilepsy, meanwhile from 69 children with abnormal EEG, 30 children (90,9%) have controlled epilepsy and 39 children (92,9%) have uncontrolled epilepsy. The result of Chi Square test is p-value 1,000 (p>0,05). Based on those data, it can be concluded that there is no correlation between initial EEG features and epilepsy outcomes in children with epilepsy at Abdul Moeloek Hospital Lampung Province, Indonesia..

Table 7. Correlation Between Antiepileptic Drug Therapy and Epilepsy Outcomes at Abdul Moeloek Hospital Lampung Province, Indonesia.

OAE Therapy	Epilepsy Outcome				P
	Controlled		Un-controlled		
	n	%	n	%	
1 OAE	29	87,9	25	59,5	0,014
≥2 OAE	4	12,1	17	40,5	
Total	33	100%	42	100%	

Table 7 shows from 54 children were given 1 OAE therapy, 29 children (87,9%) have controlled epilepsy and 25 children (59,5%) have uncontrolled epilepsy, meanwhile from 21 children who were given >2 OAE therapy, 4 children (12,1%) have controlled epilepsy and 17 children (40,5%) have uncontrolled epilepsy. The result of Chi Square test is p-value 0,014 (p<0,05). Based on those data, it can be concluded that there is a correlation between OAE therapy and epilepsy outcomes in children with epilepsy at Abdul Moeloek Hospital Lampung Province, Indonesia..

Table 8. Correlation Between Neurological Deficit and Epilpesy Outcomes at Abdul Moeloek Hospital Lampung Province, Indonesia.

Neurogical Deficit	Epilepsy Outcome				*P*
	Controlled		Un-controlled		
	n	%	n	%	

There isn't	28	84,8	32	76,2	0,03
There is	5	15,2	10	23,8	
Total	42	100%	33	100%	

Table 8 shows from 60 children with no neurological deficit, 28 children (84,8%) have controlled epilepsy and 32 children (76,2%) have uncontrolled epilepsy, meanwhile from 15 children with neurological deficit, 5 children (15,2%) have controlled epilepsy and 10 children (15,2%) have uncontrolled epilepsy. The result of Chi Square test is p-value 0,522 (p>0,05). Based on those data, it can be concluded that there is no correlation between neurological deficit and epilepsy outcomes in children with epilepsy at Abdul Moeloek Hospital Lampung Province, Indonesia..

Then, proceeding with multivariate analysis which aims to determine the factors associated with epilepsy at Abdul Moeloek Hospital Lampung Province, Indonesia. with logistic regression analysis, as follows:

Table 9. Logistic Regression Analysis Between Risk Factors and Epilepsy Outcomes.

Variable	B	SE	P	EXP(B)	CI 95%	
Initial Seizure Frequency	2,674	,626	,000	14,500	4,253	49,437

1. The Age of Seizure Onset

The result of the study based on the frequency of the age of seizure onset distributions shows there are 57 children (76%) with age of seizure onset >1 year and 18 children (24%) with age of seizure onset <1 year. This shows that the largest number of research sample are children with the age of seizure onset >1 year. This study is supported by a research conducted by Istiana *et al.*, [8] that the highest percentage of seizure onset variable is the age of seizure onset >1 year with the number of 24 children (51,1%).

The result of bivariate analysis regarding the age of seizure onset is p-value 0,439 (0>0,05), which means that there is no correlation between the age of seizure onset and epilepsy outcomes in children with epilepsy. Another study conducted by Mangunatmadja *et al.*, [9] showed different result, where a p-value was <0,001 (p<0,05). indicating that there is a correlation between the seizure onset age of <1 year and epilepsy outcomes.

The age of seizure onset is the age when the patient first experienced a seizure. The age of seizure onset becomes an important factor that potentially influence the brain activities and connectivity due to the disease interaction with normal developmental changes. Furthermore, the effect of early seizure onset is becoming an important feature to understanding the effect of epilepsy and its treatment on cognition and behavior. The main explanation for this is that the mature brain has less neuroplasticity, allowing late seizure onset to cause permanent damage on cogitive function. Neuroplasticity is associated

with early seizure onset, which is like a double edge sword, as it has been shown that early seizure onset can disrupt brain maturation development resulting in cognitive impairment and retardations [9].

Based on the statement above, indirectly said that there is a correlation between the age of seizure onset and epilepsy outcome, but in this study, the result shows that there is no correlation between the age of seizure onset and epilepsy outcome due to the large population at the age of seizure onset in children of >1 year, with the number of 57 children (76%).

2. Initial Seizure Frequency

The result of the study based on seizure frequency distribution shows there are 43 children (57,3%) with seizure frequency <5 times per day and 32 children (42,7%) with seizure frequency >5 times per day. This shows that the largest number of research sample are children with seizure frequency ,5 times per day. This study is supported by a research conducted by Mangunatmadja *et al.*, [9] that the highest percentage of seizure frequency variable is seizure frequency of <5 times per day as many as 79 children (77%).

The result of bivariate analysis regarding the early seizure frequency variable is p-value 0,000 (p<0,05) which means there is a correlation between early seizure frequency and epilepsy outcomes in children suffering from it. This is in line with a research conducted by Mangunatmadja *et al.*, [9] where p-value was <0,001 (p<0,05). Another in line research was conducted by Saygi *et al.*, [10] where p-value was <0,001 (p<0,05).

The seizure frequency may be related to the dysfunction and underlying brain pathology so it can determine the outcome of uncontrolled seizure. The high seizure frequency at the beginning will damage the nerve cells and the greater possibility of uncontrolled epileptic outcome [11].

3. Seizure Types

The result of the study based on the frequency of seizure types distribution shows there are 36 children (48%) with focal seizure and 39 children (52%) with common seizure. This shows that the largest number of research sample are children with common seizure. This study is supported by a research conducted by Istiana *et al.*, [8] that the highest percentage of seizure types variable is common seizure, as many as 43 children (91,5%).

The result of bivariate analysis regarding seizure types variable is p-value 0,03 (p<0,05) which means there is a correlation between seizure types and epilepsy outcomes. This is in line with a research conducted by Ayca *et al*., [12] where p-value was 0,000 (p<0,05). Another in line research was conducted by Asaduzzaman *et al.*, [13] where p-value was 0,028 (p<0,05).

Epileptic seizure is a temporary behavioral changes that may be an objective signs or subjective symptoms, such as: consciousness loss, stiffness, jerking/jolting that are caused by excessive or abnormal synchronous neuronal

activities in the brain resulting in focal seizure (when neuronal activity appears in one or more local brain regions or hemispheres), common (when abnormal neuronal activity begins in a widespread distribution in both hemisphere). These make seizure types become one of the factors In epilepsy outcome. The choice of first line antiepileptic drugs should be based on the clinical impression whether the patient has focal or common epilepsy. Failure to recognize the common epilepsy syndrome dan to select the right medication are the common causes for repetitive epilepsy [15].

4. Developmental Delay

The result of the study based on developmental delay distribution shows there are 63 children (84%) do not have any developmental delays and 12 children (16%) have developmental delays. This shows that the largest number of research sample are children with no developmental delays. This study is supported by a research conducted by Bhagyalakshmi, [17] that the highest percentage is 86 children (68,2%) with no signs of developmental delays.

The result of bivariate analysis regarding the developmental delay variable is p-value 0,621 (p>0,05) which means there is no correlation between developmental delays and epilepsy outcome in children suffer from it. This is in line with a research conducted by Istiana *et al*., [8] where p-value was 0,244 (p>0,05). Another not in line research was carried out by Saygi *et al.*, [10] where p-value was <0,001 (<0,05) which showed that there is a correlation between developmental delays and epilepsy outcomes.

Developmental delays occur when a child does not reach developmental milestone compared to children with the same age range [17]. Developmental delays is one of the variable to explain neurodevelopmental history and clinical status [12].

Developmental delay status is related to the abnormality in cerebral cortex structures. Children with developmental delay are at risk of experiencing severe epilepsy otcomes [10]. There are several opinions that the disrupted developmental delay in epilepsy patient can occur in the beginning of the disease or after the disease has been going on for a while and develops into an uncontrolled epilepsy [18]. A research carried out by Mangunatmaja *et al*., [9] showed there is no correlation in early gross motor skills status and there is a correlation in the evolution of gross motor skill status.

In this study shows there is no correlation between developmental delay and epilepsy outcomes, so it can be concluded that the results of this study strengthen the opinion that developmental delay occur more often after the disease has been going on for a while.

5. Early Electroencephalography (EEG) Features

The result of the study based on the frequency of early electroencephalography (EEG) features distribution shows there are 6 children

(8%) with normal EEG and 69 children (92%) with abnormal EEG. This shows that the largest number of research sample are children with abnormal EEG. This study is supported by a research conducted by Istiana *et al*., [8] that the highest percentage of early EEG variable is 30 children (63,8%) (Istiana, Sucipto, & Mangunatmadja).

The result of bivariate analysis regarding early electroencephalography variable is p-value 1,000 (>0,05) which means there is no correlation between early EEG and epilepsy outcomes in children suffer from it. This is in line with a research carried out by Istiana *et al*., where p-value was 0,546 (>0,05). Another research that is not in line was conducted by Ayca *et al*., [12] where p-value 0,000 (<0,05) which means there is a correlation between early EEG and epilepsy outcomes.

If the excitation exceeds the inhibition, the brain tissues will become hyperexcited that will lead to low seizure threshold resulting in hyper-synchronization. Neuronal cells hyper-synchronization occurs when the excitation mechanism is more dominant. If this hyper-synchronized activity of neuronal cells happen continuously, there will be more neuronal cells activated and cause epilepsy. Hyper-synchronization can give abnormal characteristic to electroencephalogram [19]. The abnormal EEG and the identified etiology are associated with an increased risks of seizure recurrence. More specifically, the abnormal finding of common or focal epileptiform discharges is associated with an approximately two times greater risk of seizure recurrence [20].

Based on the statements above, indirectly said that there is a correlation between early electroencephalography (EEG) features and epilepsy outcomes, but in this study shows that there is no correlation between early EEG features and epilepsy outcomes due to the large population of children with abnormal early EEG, as many as 69 children (92%).

6. Antiepileptic Drug (OAE) Therapy

The result of the study based on antiepileptic drug (OAE) therapy shows there are 54 children (72%) received 1 OAE treatment and 21 children (28%) received >2 OAE treatments. This shows the largest number of research sample is children who received 1 OAE treatments. This study is supported by a research conducted by Bhagyalakshmi, [16] that the highest percentage of OAE therapy variable is children who received 1 OAE teartment as many as 68 children (53,9).

The result of bivariate analysis regarding OAE therapy variable is p-value 0,014 (<0,05) which means there is a correlation between OAE therapy and epilepsy outcomes. This is in line with Neligan *et al*., [21] in his research, p-value was 0,01 (<0,05). Another in line research was carried out by Schraegle & Titus,[22] with p-value 0,014 (<0,05) which means there is a correlation between OAE therapy and epilepsy outcomes.

The definition of child epileptic therapy failure is if there is still seizure in children who have been treated with 1 type of OAE treatment up to the maximum dose. The definition of successful therapy is based on a good response to the therapy, such as the cessation of seizure within 6 months after being given 1 type of OAE treatment [23]. Epilepsy treatment is highly suggested using monotherapy to reduce the side effect, increase compliance, and avoid drug interaction. The failure of the initial phase of therapy is greatly influencing the success of therapy and the epilepsy prognosis, so the risk of monotherapy failure should be identified as early as possible to avoid uncontrolled epilepsy [24].

7. Neurological Deficit

The result of the study based on the frequency of neurological deficits distribution shows there are 60 children (80%) who do not experience neurological deficits and 15 children (20%) who suffer from neurological deficits. This shows that the largest number of research sample is children who have no neurological deficits. This study is supported by a research conducted by Arafa *et al*., [25] that the highest percentage of neurological deficits variable is 104 children (69,3%) who do not experience neurological deficits.

The result of bivariate analysis regarding the neurological deficits variable is p-value = 0,522 (>0,05) which means there is no correlation between neurological deficits and epilepsy outcomes. This is in line with a research conducted by Del Felice *et al.*, [26] that showed p-value >0,05. Another research that is not in line was carried out by Taghdiri *et al.*, [7] where p-value 0,001 (<0,05) was obtained which shows that there is a correlation between neurological deficits and epilepsy outcomes.

Children who suffer from epilepsy experiencing neurological deficits in the form of cerebral palsy which happens most often in the first year, 61% to 74% patients are experiencing their first seizure within the first 12 months of life. The correlation between brain injury severity and epileptic seizure. Also, the possibility of therapy-resistant epilepsy increasement and the risk of developing uncontrolled epilepsy [27].

The prevalence of uncontrolled epilepsy is higher in a patient with other neurological deficits compared to those who have no such disdorders [7].

Based on the statements above, indirectly said that neurological deficits is related to epilepsy outcomes, but in this study the correlation is not proven due to the large number of children population who do not experience neurological deficits, as many as 60 children (80%).

CONCLUSION

Based on the result of related factors to the outcome of children with epilepsy research at Abdul Moeloek Hospital Lampung Province, Indonesia., the conclusions obtained as follows:

1. There is a correlation between the frequency of early seizure, the type of seizures, antiepileptic drug therapy, and epilepsy outcomes in children who suffer from the disease at Abdul Moeloek Hospital Lampung Province, Indonesia..
2. Based on the result of multivariate analysis test, children who experience initial seizure frequency >5 times per day is having the risk of developing uncontrolled epilepsy 14 times higher than those who do not. This shows that the most influential factor in uncontrolled epilepsy phenomena at Abdul Moeloek Hospital Lampung Province, Indonesia. is children who experience seizure >5 times per day.

SUGGESTIONS

1. For Educational Institution
   It is hoped that it can become one of the health institution that can offer access and help in providing information about related factors to the outcome of children with epilepsy.
2. For Future Researchers
   - The authors suggest to conduct a study with bigger sample coverage and over a longer time, so that the level of accuracy of the study will be greater.
   - The authors suggest to conduct further study regarding the correlation of epileptiform electroencephalography changes to epilepsy outcomes.

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