

Risk factors for drug-resistant epilepsy in pediatric patients at Dr. Kariadi Hospital, Indonesia

Authors: Elvira Mulya¹; Dimas Tri Anantyo²; Mulyono²; Yetty Movieta Nancy³; Tun Paksi Sareharto^{3,*}

Affiliations: ¹Medical Faculty of Diponegoro University; ²Department of Child Health, Medical Faculty of Diponegoro University; ³Department of Child Health, Medical Faculty of Diponegoro University/Kariadi Hospital Semarang, Indonesia

ABSTRACT

INTRODUCTION: Epilepsy stands out as one of the prevalent neurological conditions, especially in children, caused by impaired brain function with the typical symptom of recurrent seizures due to the release of electrical charges from proximal brain neurons without provocation. The aim of this study is to identify the risk factors that contribute to the development of drug-resistant epilepsy (DRE) in pediatric patients with a prior history of epilepsy.

METHODS: A cross-sectional observational analytic study was carried out on pediatric patients with epilepsy at Dr. Kariadi Hospital Semarang, Indonesia by analyzing the patient's medical records. The data were analyzed with univariate and bivariate tests and presented in tabular form.

RESULTS: Based on the findings from 73 medical records collected for this study, the incidence of drug-resistant epilepsy (DRE) was identified in 58 subjects (79.5%). Bivariate analysis revealed significant risk factors associated with DRE, namely the type of anti-epileptic drugs (AEDs) used and their dosage ($p < 0.001$). Another factor shown to increase the risk of DRE was seizure frequency ($p = 0.016$).

CONCLUSION: The risk factors for the occurrence of DRE in children identified in this study include the type and dosage of anti-epileptic drugs (AEDs), as well as seizure frequency. Inadequate or inappropriate administration of AEDs may increase the likelihood of recurrent epileptic seizures and elevate the risk of developing DRE. Frequent seizures, which are commonly associated with DRE in pediatric patients, may further damage the developing brain.

Keywords: Epilepsy, drug-resistant, intractable, pediatri, anti-seizure medications, seizure, risk factors.

INTRODUCTION

Epilepsy stands out as one of the prevalent neurological conditions, especially occurring in children and it stands as the primary cause of morbidity in pediatric neurology [1,2]. Epilepsy is

caused by impaired brain function with a variety of typical symptoms such as recurrent seizures caused by the proximal and excessive release of electric charges in brain neurons without provocation [3]. The global healthcare problem in epilepsy affects up to 70 million individuals worldwide. Approximately

***Corresponding author:** Tun Paksi Sareharto, Address: Diponegoro 32A Street, Semarang, Central Java- Indonesia , Telephone number : +62 81390376677, Email address: paksi@fk.undip.ac.id; **Potential Conflicts of Interest (CoI):** All authors: no potential conflicts of interest disclosed; **Funding:** All authors: No funding was sought for this study; **Academic Integrity.** All authors confirm that they have made substantial academic contributions to this manuscript as defined by the ICMJE; **Ethics of human subject participation:** The study was approved by the local Institutional Review Board. Informed consent was sought and gained where applicable; **Originality:** All authors: this manuscript is original has not been published elsewhere; **Review:** This manuscript was peer-reviewed by three reviewers in a double-blind review process; **Type-editor:** Shane (USA).

Received: 16th May 2025; **Initial decision given:** 15th November 2025; **Revised manuscript received:** 21st November 2025; **Accepted:** 16th November 2025.

Copyright: © The Author(s). This is an Open Access article distributed under the terms of the Creative Commons Attribution License (CC BY-NC-ND) ([click here](https://creativecommons.org/licenses/by-nc-nd/4.0/)) which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. **Publisher:** Rwanda Biomedical Centre (RBC)/Rwanda Health Communication Center, P. O. Box 4586, Kigali. ISSN: 2079-097X (print); 2410-8626 (online)

Citation for this article: Elvira Mulya; Dimas Tri Anantyo; Mulyono et al. Risk factors for drug-resistant epilepsy in pediatric patients at Dr. Kariadi Hospital, Indonesia. Rwanda Medical Journal, Vol. 82, no.4, p. 25-30, 2025. <https://dx.doi.org/10.4314/rmj.v82i4.7>

80% of people with epilepsy reside in countries characterized by low and middle incomes with restricted resources [4]. Several studies have shown significant differences in the annual incidence rate between developed and developing countries. The prevalence in developed countries ranges from 3.2 to 5.5 per 1000, while in developing countries, it varies from 3.6 to 44 per 1000 [5]. The concept of drug-resistant epilepsy (DRE) was characterized by the International League Against Epilepsy (ILAE) in 2010 as the failure of accomplishing seizure free state within a period when around 30-35% of children with a prior history of epilepsy had intractable epilepsy [6].

Epilepsy remains a significant public health concern in Indonesia, with an estimated 70,000 new cases diagnosed each year and a national prevalence of 5–10 per 1,000 individuals [7]. The incidence is highest in infants and children, declines in young adults, and increases again in the elderly. In West Sumatra, particularly at RSUP Dr. M. Djamil Padang, 1,081 pediatric epilepsy cases were recorded in 2017, with numbers expected to rise annually [3]. A 2018 study at Dr. Kariadi Hospital in Semarang reported that 34.2% of children with drug-resistant epilepsy (DRE) had identifiable neurological risk factors [7].

Children diagnosed with epilepsy are inclined to experiencing physical and mental comorbidities such as anxiety and depression, which can adversely affect their quality of life. In addition, children with epilepsy have a higher risk of early death than those without epilepsy [8,9]. Epilepsy is considered refractory when the seizures occur very often or are so severe that they restrict the patient's capacity to live life fully on their terms [10].

Anti-seizure medications (ASM) are aimed at controlling seizures in people with epilepsy. Children who have been on epilepsy medication but still experience seizures after undergoing trials of at least two different ASM or in combination at optimal doses with adequate adherence, are categorized as intractable or DRE [11]. ILAE 2010 defined a DRE as the failure of two administrations of therapy that are adequate, appropriate in choice, and in accordance with the ASM administration schedule (both monotherapy and combination therapy) to attain a seizure-free state (no seizures for less than 12 months) [12]. Drug-resistant epilepsy is a pragmatic issue during the treatment of active epilepsy in children. Due to resistance to

ASM, there is no sufficient treatment response in some children with epilepsy [13].

Seizures that frequently occur and remain uncontrolled in children with epilepsy can be a significant burden for parents. This challenge is substantial as parents grapple with numerous daily issues related to epilepsy. It cannot be underestimated, as children are at high risk of experiencing behavioral, educational, work, concentration, and academic difficulties. Therefore, this study aims to examine the risk factors for DRE in children, including the age of onset, use of ASM and their dosage, attack frequency, and electroencephalography (EEG) results. The findings aim to be valuable, serving as appropriate guidelines to prevent DRE in children with a history of epilepsy.

METHODS

Study design and settings

This study employs an analytical observational approach with a cross sectional design and is conducted at Dr Kariadi Hospital, Semarang, Indonesia. Data were gathered from patient's medical records from January 1 2018 to March 31 2022, and the study was carried out from May to June 2022.

Population

The target population for this study comprised pediatric patients diagnosed with epilepsy and undergoing treatment at Dr. Kariadi General Hospital Semarang, Indonesia, involving 73 subjects. Subject selection in this study employed a consecutive sampling method, in which all patients meeting the inclusion criteria were recorded until the required sample size was achieved. The sample size was determined based on the number of pediatric patients with a history of epilepsy at RSUP Dr. Kariadi Semarang. All study subjects met the inclusion criteria, which included pediatric patients undergoing treatment and diagnosed with epilepsy at the pediatric clinic of Dr. Kariadi Hospital, Semarang, Indonesia. Subjects had to be pediatric patients diagnosed with epilepsy, regularly taking ASM with more than two types of drugs for 12 months or more, and patients with complete medical records.

Data sources and categorisation

In this study, the data were obtained from the

patient's medical records and the anti-epileptic drugs (AEDs) used by patients were classified into two categories: monotherapy using first-line AEDs and polytherapy. Dosage comparisons for each patient were assessed based on the mg/kg/day range. Seizure frequency was categorized as infrequent or frequent, with the latter defined as experiencing seizures at a frequency of >1 episode per week. All subjects underwent EEG examination and were categorized as either normal (no epileptiform discharges detected) or abnormal (presence of epileptiform discharges identified).

Data analysis

The data underwent analysis utilizing the IBM SPSS Statistics 25 for Windows and Microsoft Excel computer programs. Statistical analysis was carried out in the following steps: Univariate analysis was conducted to determine the profile of the research subjects, and the data were presented in the form of frequencies.

Table 1: Subject's characteristics

Variable	Frequency	%
Gender		
Male	36	49.3
Female	37	50.7
Age		
< 5 years old	8	11.0
> 5 years old	65	89.0
Therapy outcome		
Non-drug-resistant	15	20.5
Drug-resistant	58	79.5
Age of onset		
> 1 year old	54	74.0
< 1 year old	19	26.0
ASM and dosage		
First line	13	17.8
Second line	60	82.2
Frequency of seizure		
Rare	24	32.9
Frequent	49	67.1
Electroencephalogram		
Normal	6	8.2
Abnormal	67	91.8

Bivariate analysis was performed using the Fischer exact test and the Mann Whitney test.

Ethical considerations

The research was conducted after obtaining Ethical Clearance from the Medical and Health Research Ethics Commission (KPEK) Faculty of Medicine, Diponegoro University number 128/EC/KEPK/FK-UNDIP/V/2022. The research was carried out with permission from the involved party and authorization for accessing patient medical records at RSUP Dr. Kariadi Semarang, Indonesia. The identity of the research subjects and the obtained data are kept confidential and used solely for research purposes.

RESULTS

The subjects of this study consisted of 73 patients, 36 patients (49.3%) were male and 37 patients (50.7%) were female. 8 patients were <5 years of age and 65 patients were >5 of age. Analysis of characteristics of the subjects found that 58 subjects (79.5%) had DRE and 15 subject (20.5%) had non-DRE. Age of onset categorized into two types, which is > 1 year with 54 subjects (74.0%) and < 1 year with 19 subjects (26.0%). Based on the ASM and the doses were also categorized into two types, namely the first line, with 13 subjects (17.8%), and the second line, with 60 subjects (82.2%). The frequency of seizures in children with epilepsy was divided into two categories: rare, with 24 subjects (32.9%), and frequent, with 49 subjects (67.1%) (Table 1). Based on the EEG results, it was categorized into two types, general seizure, with 6 subjects (8.2%) and focal seizure, with 67 subjects (91.8%).

The table 2 shows that there were 43 subjects with onset age of > 1 year and 15 subjects with onset age of < 1 year. The P value of 0.593 is greater than 0.05 which suggests that it isn't significant, or age of onset isn't a risk factor for DRE in children. Data of ASM usage and dosage showed 5 subjects with the first line of ASM and 53 subjects with the second line of ASM. The p value <0.001 is less than 0.05 which means it is significant or ASM usage and dosage are risk factor for the incidence of DRE in children. Regarding the variable frequency of attacks, 15 subjects were found with rare frequencies and 43 subjects were found at frequent frequencies. The p value of 0.016 is less than 0.05 which means it

Table 2. Test results for the relationship of risk factors with therapy outcomes

Variable	Drug-resistant epilepsy (n=58)	p value	RR (95% IC)
Age of Onset			
> 1 year old	43 (74.1%)	0,593 [£]	1,01 (0,77 – 1,73)
< 1 year old	15 (25.9%)		
ASM and dosage			
First Line	5 (8.6%)	<0,001 ^{£*}	0,44 (0,22 – 0,87)
Second Line	53 (91.4%)		
Frequency of Seizure			
Rare	15 (25.9%)	0,016 ^{£*}	0,71 (0,51 – 0,99)
Frequent	43 (74.1%)		
Electroencephalogram			
General	5 (8.6%)	0,642	1,05 (0,72 – 1.54)
Focal	53 (91.6%)		

* Significant ($p < 0,05$); £ Fisher's exact

is significant or the frequency of attacks is a risk factor for the incidence of DRE in children. The EEG result variables were divided into two categories, namely normal and abnormal. In normal EEG there were 5 subjects and in abnormal EEG there were 53 subjects. The p value of 0.642 is greater than 0.05, indicating that the EEG results are not a significant risk factor for DRE in children.

Fisher's exact test showed that the ASM usage and the dose, and frequency of attacks were factors that significantly influenced the occurrence of DRE in children. The relative risk for ASM usage and the dose was 0.44 with a significance value showing $p \leq 0.001$ ($p \leq 0.05$) and a relative risk of 0.71. The results of the attack frequency analysis with a significance value showed $p = 0.016$ ($p \leq 0.05$), with a 95% confidence level, the RR value was considered significant.

DISCUSSION

The Fisher's exact test in this study defined that the age of onset did not show significant results, or it could be said that the age of onset was not a risk factor for DRE in children ($p=0.593$). These findings align with a research study by Gusta et al., which stated that the age of onset had no effect on the incidence of DRE in children [7]. However, a study by Oncu et al. found different result, stating that the age of onset had an effect on the occurrence of

DRE in children. Seizure attacks in children before reaching the age of 1 is a factor in the occurrence of DRE in children [11].

Research by Ayça et al. explained that 50% to 60% of patients with DRE experience seizures within the initial year of life. The onset of seizures within the first year of life influences the development of the immature brain. This research found that 65.6% DRE patients experience their first seizure before the age of 1 year [6].

The results of this study showed that the use of ASM and their dosage were the factors that most influenced the incidence of DRE in children. In this study, it was observed that more children with a history of DRE had taken second-line ASM. Fisher's exact test demonstrated that the use of ASM and its dosage had a significant relationship to the incidence of DRE in children ($p \leq 0.001$). This research is in accordance with research by Siallagan, which explains that the ASM factor significantly influences the success of subsequent therapy and the prognosis of epilepsy. This study included subjects with seizure frequency ≥ 5 times a month after receiving ASM monotherapy and had the opportunity to become polytherapy [14]. Administering ASM and determining their dosage as first-line or monotherapy is an approach for newly diagnosed patients. If the first line proves ineffective or cannot suppress epileptic seizures, then second-line drugs can be introduced while

maintaining the use of the first-line ASM [15]. This study aligns with Moosa et al. which explained that a few ASMs are considered broad-spectrum drugs as they are effective against various types of seizures. However, some ASMs are known to be ineffective for certain types of seizures and can worsen epileptic seizures. The mechanism of action is an important factor in the selection of first-line and second-line drugs, as drugs with the same mechanism of action can cause synergistic side effects. The type of ASM, including the determination of the number of doses per day, and the usage of drugs that are not suitable for children with a history of epilepsy can prevent the development of DRE in children [16].

This study demonstrates a significant correlation between the frequency of seizures and the incidence of DRE in children. Research in Bangladesh yielded similar results, where frequent seizure frequency, defined as ≥ 1 per day, was identified as an independent predictor of DRE in children. The frequency of seizures itself can further damage the developing brain [17].

A study in Turkey defined the frequency of seizures experienced by pediatric patients as frequent if occurring once a day and as rare if less than once a week. The study concluded that patients are more likely to achieve a favorable result, namely a seizure free state, if they experience rare frequencies, conversely, frequent frequencies can result in DRE in children [1]. Research conducted by Falco-Walter et al. explained that when a person experiences an epileptic seizure, the brain exhibits a pathological tendency, and lasts a long time until it has recurrent seizures. More particularly, epilepsy is analyzed when a individual has at least two reflex seizures separated by more than 24 hours and likely experiences another seizure with a similar risk of generalized recurrence despite ASM administration [18].

This study used the Fisher's exact test, which showed that the EEG results were not significant ($p = 0.642$). This results of this study are not in accordance with the research by Jayalakshmi et al., which explains that epilepsy with structural abnormalities, such as focal cortical dysplasia, is considered as one of the causes of DRE [19]. Research by Engel et al. also reported that DRE is associated with hippocampal sclerosis (structural disorder) that usually manifest as focal EEG results [20].

This study has some limitations. First, the sample

size was relatively small because the data were obtained from a single center. Second, the categorization of DRE patients based on therapy and EEG findings was relatively simplified. Additionally, there is a possibility that other relevant risk factors were not assessed.

CONCLUSION

The results of this research and the discussion of the risk factors for the occurrence of DRE in pediatric patients at Dr. Kariadi Hospital, Semarang, Indonesia, the following conclusions are obtained: Age of onset is not a risk factor for DRE in children, ASM use and dosage are risk factors for DRE in children and seizure frequency is a risk factor for DRE in children. We recommend that future studies further expand and explore the topics addressed in this research by incorporating more detailed classifications of DRE patients and evaluating additional factors that may influence the progression of epilepsy, such as etiology, socioeconomic status, and adherence to medication.

REFERENCES

1. Hirfanoglu, T.; Serdaroglu, A.; Kurt, G.; Erdem, A.; Capraz, I.; Bilir, E.; et al. Outcomes of resective surgery in children and adolescents with focal lesional epilepsy: The experience of a tertiary epilepsy center. *Epilepsy Behav* 2016, 63, 67-72, doi:10.1016/j.yebeh.2016.07.039.
2. Ganda, C.; Rita, E. Kejadian epilepsi pada anak dengan riwayat kejang demam pada tahun 2014-2019: studi literatur. <https://repositori.usu.ac.id/handle/123456789/30666> (accessed on 15 November 2022).
3. Khairin, K.; Zeffira, L.; Malik, R. Karakteristik penderita epilepsi di bangsal anak RSUP Dr. M. Djamil Padang tahun 2018. *Heal Med J* 2020, 2, 16-26, doi: 10.33854/heme.v2i2.453.
4. Trinka, E.; Kwan, P.; Lee, B.; Dash, A. Epilepsy in Asia: Disease burden, management barriers, and challenges. *Epilepsia* 2019, 60, 7-21, doi:10.1111/epi.14458.
5. Alshahawy, AK.; Darwish, AH.; Shalaby, SE.; Mawlana, W. Prevalence of idiopathic epilepsy among school children in Gharbia Governorate, Egypt. *Brain Dev* 2018, 40, 278-286, doi:10.1016/j.braindev.2017.12.009.
6. Ayça, S.; Oral, RD.; Dündar, PE.; Polat, M.

- Six clinical predictors for intractable childhood epilepsy. *J Pediatr Res* 2019, 6, 213-219, doi:10.4274/jpr.galenos.2019.93276.
7. Yolanda, NGA.; Sareharto, TP.; Istiadi, H. Faktor faktor yang berpengaruh pada kejadian epilepsi intraktable anak di RSUP Dr. Kariadi Semarang. *Jurnal Kedokteran Diponegoro* 2019, 8, 378-389, doi:10.14710/dmj.v8i1.23369.
8. Hingray, C.; McGonigal, A.; Kotwas, I.; Micoulaud, J. The relationship between epilepsy and anxiety disorders. *Curr Psychiatry Rep* 2019, 21, 1-13, doi:10.1007/s11920-019-1029-9.
9. LaGrant, B.; Marquis, B.; Berg, AT.; Grinspan, Z. Depression and anxiety in children with epilepsy and other chronic health conditions: National estimates of prevalence and risk factors. *Epilepsy Behav* 2020, 103, 1-21, doi:10.1016/j.yebeh.2019.106828.
10. Asaduzzaman, M.; Rahman, MM.; Hasan, MN. Clinical predictors of poorly-controlled childhood epilepsy: A case-control study. *Med Today* 2020, 32, 85-90, doi:10.3329/medtoday.v32i2.48819.
11. Oncu, D.; Ozcelik, AA.; Adanir, SS. Risk factors in childhood intractable epilepsy. *Eur J Ther* 2021, 27, 78-83, doi:10.5152/eurjther.2021.20003.
12. Kwan, P.; Arzimanoglou, A.; Berg, AT.; Brodie, MJ.; Hauser, WA.; Mathern, G.; et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc task force of the ILAE Commission on Therapeutic Strategies 2010, 51, 1069-1077, doi:10.1111/j.1528-1167.2009.02397.x.
13. Hwang, ST.; Stevens, SJ.; Fu, AX.; Proteasa, SV. Intractable generalized epilepsy: Therapeutic approaches. *Curr Neurol Neurosci Rep* 2019, 19, 1-10, doi:10.1007/s11910-019-0933-z.
14. Wijaya, JS.; Saing, JH.; Lubis, BM. Faktor-faktor yang mempengaruhi pemberian politerapi obat antiepilepsi (OAE) pada anak penderita epilepsi. <http://repositori.usu.ac.id/handle/123456789/16928> (accessed on 15 November 2022).
15. Dijkman, SC.; Alvarez, R.; Danhof, M.; Pasqua, OD. Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go. *Expert Opin Drug Metab Toxicol* 2016, 12, 1143-1156, doi:10.1080/17425255.2016.1203900.
16. Moosa, ANV. Antiepileptic drug treatment of epilepsy in children 2019, 25, 381-407, doi:10.1212/CON.0000000000000712.
17. Moinuddin, AKM.; Rahman, MM.; Akhter, S.; Kawser, CA. Predictors of childhood intractable epilepsy- a retrospective study in a tertiary care hospital. *Bangladesh J Child Heal* 2009, 33, 6-15, doi:10.3329/bjch.v33i1.5669.
18. Falco, JJ.; Scheffer, IE.; Fisher, RS. The new definition and classification of seizures and epilepsy. *Epilepsy Res* 2018, 139, 73-79, doi:10.1016/j.eplepsyres.2017.11.015.
19. Jayalakshmi, S.; Nanda, SK.; Vooturi, S.; Vadapalli, R.; Sudhakar, P.; Madigubba, S.; et al. Focal cortical dysplasia and refractory epilepsy: Role of multimodality imaging and outcome of surgery. *Am J Neuroradiol* 2019, 40, 892-898, doi:10.3174/ajnr.A6041.
20. Engel, J. Approaches to refractory epilepsy. *Ann Indian Acad Neurol* 2014, 17, 12-17, doi:10.4103/0972-2327.128644.