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Drug-Resistant Epilepsy: A Retrospective Observational Study at a Tertiary Care Hospital

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Abstract:

Objective: To determine the prevalence and predictors of drug-resistant epilepsy among patients with epilepsy. **Methodology:** A retrospective observational study was conducted at the Neurology Department of Liaquat National Hospital, Karachi, for the period from November, 2024 to October, 2025. Patients with epilepsy were enrolled, excluding neonates and those with psychiatric comorbidities or active substance abuse. Participants were recruited consecutively. Descriptive statistics summarized patient characteristics, while chi-square tests evaluated associations between variables such as drug adherence, epilepsy type, and antiepileptic drug (ASM) selection. Odds ratios (ORs) with 95% confidence intervals were calculated to quantify the strength of these associations.

Results: A total of 382 participants were included (49.5% male, 50.5% female), with a mean age of 31.73 +/- 16.82 years and a mean seizure onset age of 25.3 years. The majority were urban residents with higher educational levels and 19.4% had refractory epilepsy. On multivariate logistic regression analysis, normal MRI brain findings (a OR = 0.29, 95% CI: 0.142–0.570; $p < 0.001$), normal EEG findings (a OR = 0.50, 95% CI: 0.256–0.974; $p = 0.042$) and adherence to the given treatment (a OR= 0.516, 95% CI: 0.234-1.138; p=0.101) have lower odds of having drug resistance. Lower level of education (a OR = 3.496, 95% CI: 1.687–7.245; $p < 0.001$), and a history of status epilepticus (a OR = 8.029, 95% CI: 4.186-15.400: $p <0.001$) have higher odds of refractory epilepsy.

Conclusion: By identifying key predictors of drug-resistant epilepsy, our study contributes to a better understanding of factors associated with treatment resistance and may inform future interventions.

Keywords: Drug-Resistant Epilepsy, Tertiary Care Centers, Treatment Adherence and Compliance, Unemployment, Urban Population.

Introduction

Epilepsy in Pakistan has a crude prevalence rate of 9.98 per 1,000 population and is twice as common in rural areas.[1] About one-third of patients with epilepsy are considered to have drug-resistant epilepsy, defined as an inability to attain sustained seizure freedom after trials of two appropriately chosen and tolerated antiepileptic drug regimens, whether used alone or in combination. Patients with refractory epilepsy face a high disease burden, with notable disability and impaired quality of life.[2]

A recent study states that globally; DRE is estimated to affect approximately 30–40% of individuals with epilepsy.[3] In contrast, an Indian cohort of 2,153 epilepsy patients observed a relatively lower proportion of drug-resistant cases, estimated at 11.3%.[4] However, there is limited data on the prevalence of drug-resistant epilepsy in Pakistan. A study conducted at the Children's Hospital Lahore showed a prevalence of 0.3%.[5]

Several factors have been linked to drug-resistant epilepsy, including history of status epilepticus, infantile spasms, neonatal seizures, microcephaly, frequent seizures before treatment, poor response to initial therapy, abnormal neurological status, early breakthrough seizures, developmental delay, neurological deficits, high seizure frequency at onset, and abnormal brain imaging.[6] Additionally, non-adherence to medication regimens is another important factor in the development of refractory epilepsy. Non-adherence might be due to drug side effects or significant compliance issues related to myths associated with drug use, especially among the young female population.

In underdeveloped countries like Pakistan, polypharmacy is quite common, with underdosing of multiple medications, calling the epilepsy drug resistant or refractory. Surgical options for refractory epilepsy are limited in Pakistan, with only a few centers offering epilepsy surgery. The lack of availability of epilepsy surgery in Pakistan is a major barrier to effective management of refractory epilepsy.[7-9] This study provides single-centre data on the clinical characteristics and factors associated with DRE, which may help improve understanding of DRE in our setting.

Methodology

A retrospective review of outpatient department (OPD) records was conducted for the period from November 2024 to October 2025.

Ethical approval: The study was approved by the Liaquat National Hospital Ethics Review Committee (ERC approval number#1092-2024-ERC-LNH; dated: October 31, 2024).

It included all consecutive patients with a neurologist-confirmed diagnosis of epilepsy for at least one year, presenting to the neurology outpatient department, across all age groups except neonates. Patients with newly diagnosed epilepsy and those with known comorbid psychiatric illnesses or substance abuse were excluded. Similarly, patients with symptomatic seizures due to electrolyte imbalance or hypoglycemia, as well as those with psychogenic non-epileptic seizures, were also excluded.

The patients were divided into two groups based on the definition of ILAE as DRE and non-DRE. Drug-resistant epilepsy was operationally defined as the failure to achieve seizure control for 12 months, with at least two appropriately chosen and adequately dosed anti-epileptic drugs (ASMs), used either as monotherapy or in combination. The non-DRE are the ones who were seizure-free for 12 months on current antiepileptic regimen.[10]

Abnormal MRI was defined as the presence of structural brain lesions relevant to epilepsy, including hippocampal sclerosis, cortical malformations, gliosis, encephalomalacia, tumors, vascular malformations, or other focal structural abnormalities. Abnormal EEG was defined as the presence of interictal epileptiform discharges (spikes, sharp waves, spike-and-wave complexes), with or without associated focal or generalized slowing.

The sample size was calculated using the WHO sample size calculator, estimated prevalence of drug-resistant epilepsy 35%[11] (P = 0.45), with a 95% confidence interval and a 5% margin of error, resulting in a required sample size of 349 cases. To account for potential incomplete or missing records, the sample size was increased by 10%, resulting in a final required sample of 382. Due to the retrospective design of the study, the requirement for informed patient consent was waived. Patients were identified through the hospital record system using the diagnosis of epilepsy. The medical record numbers (MRNs) of all patients labelled with epilepsy, generalized epilepsy, focal or partial epilepsy and unspecified or unknown origin were retrieved, and the corresponding clinical files were reviewed in detail.

Data was extracted using a structured form developed based on variables reported in prior literature on drug-resistant epilepsy. The form included demographic characteristics, clinical features, investigation findings, and treatment-related variables relevant to the study

objectives. Data extraction from the medical records was performed by a trained undergraduate research assistant, who recorded the information as documented in the patient files, and any uncertainties were reviewed by the investigators.

Prior anti-seizure medication (ASM) trials were retrospectively verified from the patients' OPD and medical records. For each previously used ASM, the dedicated medication section of the OPD record was reviewed for the drug name, prescribed dose, and duration of treatment; treatment response and reasons for discontinuation were also recorded when documented. The adequacy of previous ASM trials was assessed from these documented treatment details, with serial OPD records used for corroboration where available. Information from medical records, including demographic, clinical, EEG, and MRI findings, was entered into Google Forms and subsequently exported to a secure Excel sheet. Any missing or ambiguous data was clarified through follow-up phone calls with the patients or caregivers.

Statistical analysis: Data were analyzed through SPSS v 27. Descriptive statistics were used to calculate means and standard deviations. Chi-square test was applied to examine associations between categorical variables. Multivariable logistic regression was performed to identify factors independently associated with drug-resistant epilepsy, which included demographics, type of epilepsy, history of status epilepticus, MRI brain and EEG findings, ASM-related side effects and selection of ASMs according to seizure type. P- value of <0.05 was considered statistically significant.

Results

The study included 382 participants with a near-equal distribution between males (49.5%) and females (50.5%). The mean age of participants was 31.73 +/- 16.82 years. The participants were predominantly young adults, with the largest proportion aged 15–25 years (41.9%), followed by those aged 26–40 years (28.5%).

Children younger than 14 years constituted only 5.5% of the study population, indicating that epilepsy in this cohort was largely represented among adolescents and adults. In terms of marital status, the percentage of people who had never married was slightly higher (51.6%) compared to those who were married. The overall level of education was relatively high, with 40.1% of participants having attained higher education, while only 3.4% had no formal education. Occupationally, students constituted the largest proportion (35.1%), followed by housewives (24.9%) and employed persons (24.3%).

Most participants lived in cities (89.5%) and nearly all used healthcare services (98.2%). Primary generalized epilepsy was the most prevalent, affecting 67.5% of the participants, with focal epilepsies (with or without impaired awareness) representing a smaller percentage. Status epilepticus was observed at 12.6%. MRI was abnormal in 19.6% of cases, while EEG findings were abnormal in 28.6%. A family history of epilepsy was reported in 5.8% of participants, head trauma in 5.2%, and focal motor deficits in 4.7% of the study population. Regarding treatment outcomes, 79.8% of patients demonstrated a reduction in seizure frequency after the last antiepileptic drug taken within the previous year.

A high rate of treatment adherence (91.4%) was reported. Among the 8.6% who were non-adherent, the most common reason cited was forgetfulness (21.2%). The median seizure frequency decreased from two before treatment to zero at present, reflecting good seizure control. The median duration of epilepsy was four years, and the median seizure-free interval was 12 months. Table-I.

Side effects of Antiseizure medicine were reported by 14.1% of participants. The most prevalent side effects were behavioral, including depression or agitation, reported by 55.6% of those experiencing side effects. Other notable side effects included hair fall (14.8%) and sedation (5.6%). Treatment-related adverse effects are shown in Fig.1.

A total of 74 patients (19.4%) were identified as having drug resistant epilepsy. Several factors showed a statistically significant association ($p<0.05$) with refractoriness: A history of status epilepticus ($p < 0.001$), focal motor deficits ($p = 0.011$), and

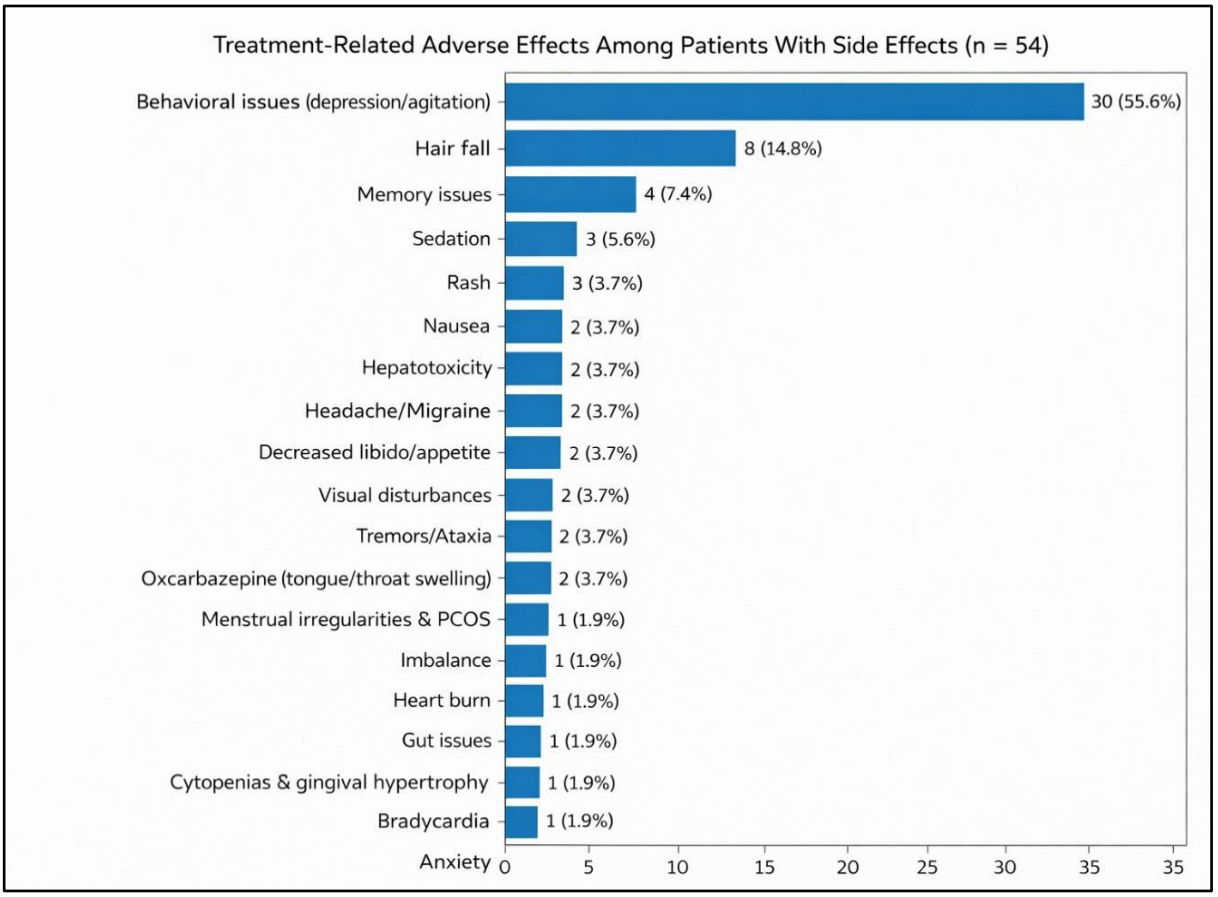

Fig.1: Shows the treatment-related adverse effects.

Table-I: summarizes continuous variables related to age and epilepsy characteristics using the median (interquartile range) and mean ± standard deviation.

	Median (Q1-Q3)	*Mean±Std. Dev*
Age (years)	25.00(19.75-40.00)	31.73±16.82
Age at onset of first seizure (years)	20.00(14.00-32.00)	25.28±16.95
Seizure frequency before Treatment (seizures per month)	2.00(1.00-3.00)	2.63±3.88
Current seizure frequency (seizures per month)	0.00(0.00-0.25)	0.85±2.82
Duration of epilepsy (years)	4.00(2.00-8.25)	6.52±7.32
Longest seizure-free interval (months)	12.00(6.00-24.00)	22.60±34.00

delayed milestones ($p = 0.035$) were significantly more common in the refractory group. Abnormal MRI ($p < 0.001$) and abnormal EEG results ($p < 0.001$) were strongly associated with refractory cases. Socioeconomic factors, including lower education levels (no formal education) and unemployment, were also significantly associated with refractory epilepsy ($p = 0.032$ and $p = 0.026$, respectively). Patients with refractory epilepsy were significantly more likely to experience treatment side effects ($p < 0.001$) and reported lower rates of seizure frequency reduction ($p < 0.001$). Comparison between the two groups shown in Table-II. On multivariable logistic regression analysis, normal MRI brain findings have lower odds of drug-resistant epilepsy compared with abnormal MRI findings (aOR 0.285, 95% CI: 0.142–0.570; $p < 0.001$). Similarly, normal EEG findings have lower odds of drug-resistant epilepsy compared with abnormal (aOR 0.500, 95% CI: 0.256–0.974; $p = 0.042$).

Treatment-related side effects showed a borderline association after adjustment (aOR 2.155,

95% CI: 0.997–4.658; p = 0.051), while selection of ASM according to seizure type was no longer statistically significant after adjustment. Lower level of education (a OR = 3.496, 95% CI: 1.687–7.245; p < 0.001), and a history of status epilepticus (a OR = 8.029, 95% CI: 4.186-15.400: p <0.001) have higher odds of refractory epilepsy. Comparison of drug-refractory and non-drug-refractory epilepsy with unadjusted and adjusted odds ratios is shown in Table-III.

Discussion

Previous studies have demonstrated substantial variation in the prevalence of drug-resistant epilepsy (DRE) across different populations. A systematic review and meta-analysis reported a prevalence of 13.7% in population- or community-based cohorts compared with 36.3% in clinic-based cohorts, highlighting the influence of study setting and patient selection on prevalence estimates.[1] Other systematic reviews have reported pooled prevalence estimates of approximately 30%, although considerable heterogeneity exists between studies, partly because of differences in the definition and identification of DRE.[2] In the present study, the prevalence of DRE was 19.4%, which was at the lower end of the range reported internationally and was closer to estimates from population-based studies despite our hospital-based setting. This relatively lower prevalence may reflect differences in referral patterns, healthcare access, and the clinical spectrum of patients attending our center. Unlike highly specialized referral cohorts that may preferentially include patients with severe or refractory epilepsy, our study included a broader spectrum of patients managed in a general hospital setting.[4,10,11,12]

We identified a significant association of focal motor deficit and history of delayed milestones with DRE. These results were consistent with the prior studies, which narrated that perinatal problems were the leading cause of DRE.[12-14] This is likely attributable to underlying structural brain pathologies in this population, as well as issues related to medication adherence. Brain lesions cause neuronal damage and reactive gliosis. According to the transporter hypothesis of DRE, these structural abnormalities impair the blood–brain barrier by affecting capillary endothelial cells, leading to increased expression of efflux transporters, whereby adequate serum drug levels fail to achieve therapeutic brain concentrations.[15]

Although no robust relation was observed between seizure type and DRE, focal and secondarily generalized seizures were more frequently encountered in patients with refractory seizures, a finding that is concordant with existing literature.[16] Status epilepticus has been postulated as an independent predictor of seizure intractability. In our study, we found a notable association between status epilepticus and DRE. This may be explained by the fact that prolonged status epilepticus leads to NMDA receptor-mediated internalization of GABA receptors, resulting in reduced inhibitory GABAergic signaling and fewer receptors available for the anti-epileptic drugs,

Table-II: Comparison of drug-refractory and non-drug-refractory

	Refractory epilepsy		*p- value*
	Yes	*No*	
Gender			
Male	40(54.1)	149(48.4)	0.380
Female	34(45.9)	159(51.6)	
Age Group			

≤14 years	4(5.4)	17(5.5)	0.807
15-25 years	30(40.5)	130(42.2)	
26-40 years	25(33.8)	84(27.3)	
41-60 years	9(12.2)	51(16.6)	
>60 years	6(8.1)	26(8.4)	
Marital Status			
Ever Married	35(47.3)	150(48.7)	0.828
Never Married	39(52.7)	158(51.3)	
Education Level			
No Formal Education	6(8.1)	7(2.3)	0.032*
Primary	19(25.7)	64(20.8)	
Secondary	27(36.5)	106(34.4)	
Higher	22(29.7)	131(42.5)	
Occupation			
Employed	15(20.3)	78(25.3)	0.026*
Jobless	16(21.6)	24(7.8)	
Housewife	16(21.6)	79(25.6)	
Student	22(29.7)	112(36.4)	
Business	4(5.4)	13(4.2)	
Retired	1(1.4)	2(0.6)	
Resident			
Rural	12(16.2)	28(9.1)	0.072
Urban	62(83.8)	280(90.9)	
Access to healthcare services			
Yes	73(98.6)	302(98.1)	1.000
No	1(1.4)	6(1.9)	
Types of Epilepsy			
Focal	5(6.8)	22(7.1)	0.074
Focal with impaired awareness	7(9.5)	28(9.1)	
Secondary generalized	18(24.3)	37(12)	
Primary generalized	42(56.8)	216(70.1)	
Unclassified or unknown	2(2.7)	5(1.6)	
H/O status epilepticus			
Yes	27(36.5)	21(6.8)	<0.001*
No	45(60.8)	281(91.2)	
Not Known	2(2.7)	6(1.9)	
Risk Factors			
Mental retardation	6(8.1)	10(3.2)	0.097
Focal motor deficit	8(10.8)	10(3.2)	0.011
Perinatal insult	3(4.1)	5(1.6)	0.188
History of CNS infection	3(4.1)	7(2.3)	0.415

Febrile convulsions	2(2.7)	3(1)	0.249
Delayed milestones	6(8.1)	8(2.6)	0.035*
Head trauma	5(6.8)	15(4.9)	0.560
Family history of epilepsy	5(6.8)	17(5.5)	0.780
MRI brain (n=331)			
Normal	37(58.7)	229(85.4)	<0.001*
Abnormal	26(41.3)	39(14.6)	
EEG findings (n=364)			
Normal	35(49.3)	225(76.8)	<0.001*
Abnormal	36(50.7)	68(23.2)	
Side effects of ASMs			
Yes	20(27)	34(11)	<0.001*
No	54(73)	274(89)	
Adherence to the treatment			
Yes	64(86.5)	285(92.5)	0.096
No	10(13.5)	23(7.5)	
ASM levels assessed			
Yes	35(47.3)	99(32.1)	<0.001*
No	19(25.7)	47(15.3)	
Not applicable	20(27)	162(52.6)	
ASM Selection was according to seizure type			
Yes	67(90.5)	300(97.4)	0.013*
No	7(9.5)	8(2.6)	
Surgical interventions performed			
Yes	1(1.4)	9(2.9)	<0.001*
No	36(48.6)	54(17.5)	
Not applicable	37(50)	245(79.5)	

p-value≤0.05 considered as significant. *Significant at 0.05 levels.

Table-III: Comparison of drug-refractory and non-drug-refractory epilepsy with unadjusted and adjusted odds ratios.

	Un-Adjusted		*Adjusted*	
	p-value	*OR (95% CI)*	*p-value*	*aOR (95% CI)*
Gender				
Male	0.381	1.255(0.755-2.088)		
Female		1.000		
Age Group				
≤14 years	0.978	1.020(0.250-4.156)		
15-25 years	1.000	1.000(0.378-2.644)		
26-40 years	0.616	1.290(0.477-3.484)		
41-60 years	0.643	0.765(0.246-2.381)		
>60 years		1.000		

Marital Status				
Ever Married	0.828	0.945(0.569-1.571)		
Never Married		1.000		
Education Level				
No Formal Education	0.007*	5.104(1.568-16.614)		
Primary	0.102	1.768(0.893-3.499)		
Secondary	0.187	1.517(0.817-2.815)		
Higher		1.000		
Occupation				
Employed	0.447	0.385(0.033-4.516)		
Jobless	0.820	1.333(0.111-15.960)		
Housewife	0.471	0.405(0.035-4.741)		
Student	0.454	0.393(0.034-4.523)		
Business	0.719	0.615(0.034-4.523)		
Retired		1.000		
Resident				
Rural	0.076	1.935(0.933-4.017)		
Urban		1.000		
Access to healthcare services				
Yes	0.733	1.450(0.172-12.233)		
No		1.000		
Type of Epilepsy				
Focal	0.561	0.568(0.084-3.821)		
Focal with impaired awareness	0.616	0.625(0.100-3.924)		
Secondary generalized	0.825	1.216(0.215-6.887)		
Primary generalized	0.398	0.486(0.091-2.590)		
Unclassified or unknown		1.000		
H/O status epilepticus				
Not Known	0.378	2.081(0.407-10.634)		
Yes	<0.001*	8.029(4.186-15.400)		
No		1.000		
MRI brain (n=331)				
Normal	<0.001*	0.242(0.132-0.444)	<0.001*	0.285(0.142-0.570)
Abnormal		1.000		1.000
EEG findings (n=364)				
Normal	<0.001*	0.294(0.171-0.503)	0.042*	0.500(0.256-0.974)
Abnormal		1.000		1.000
Side effect of treatment				
Yes	<0.001*	2.985(1.598-5.574)	0.051	2.155(0.997-4.658)
No		1.000		1.000
Adherence to the treatment				
Yes	0.101	0.516(0.234-1.138)		
No		1.000		
ASM levels assessed				
Yes	<0.001*	2.864(1.566-5.237)	<0.001*	3.496(1.687-7.245)
No	0.001*	3.274(1.615-6.640)	0.115	2.077(0.837-5.155)

Not applicable		1.000		1.000
ASM Selection was according to seizure type				
Yes	0.011*	0.255(0.089-0.728)	0.221	0.402(0.094-1.731)
No		1.000		1.000
Surgical interventions performed				
Yes	0.774	0.736(0.091-5.976)		
No	<0.001*	4.414(2.559-7.615)		
Not applicable		1.000		

Binary logistic regression was applied. p-value≤0.05 considered as significant. *Significant at 0.05 levels.

therefore resulting in permanent neuronal injury, which contributes to refractoriness.[17] Although Antiseizure medicine are largely safe, neurobehavioral adverse effects remain the most prominent contributor to non-adherence. The detectable association observed with drug-resistant epilepsy in our study suggests that poor adherence may contribute to apparent treatment resistance in this subset of patients. Literature used the word pseudo-refractory for such cases.[18]

Socioeconomic factors, including lower education levels and unemployment, were markedly associated with refractory epilepsy, likely due to the high cost and limited availability of essential Antiseizure medicine in our country - a problem highlighted in local literature reporting gaps in ASM supply and the reliance on more affordable alternatives that were often less effective in controlling seizures.[19] International data indicate that this problem is not limited to developing countries. In the UK, for example, patients with lower socioeconomic status are less likely to receive consistent treatments and hence have difficulty with medication adherence. Financial hardships, health literacy and overall access to healthcare remain major contributors to the global burden, with more severe forms such as DRE and super-refractory epilepsy being increasingly observed.[20]

Strengths: One of the key strengths of this study is the use of the updated International League Against Epilepsy (ILAE) definition of DRE, which helped reduce the inconsistency reported in earlier literature.

Limitations: First, it was conducted at a single center, which may limit the generalizability of the findings. Second, data collection relied on both medical record review and follow-up phone calls, which may have introduced recall bias. Thirdly, lack of standardized ICD coding for all patient records, which may have led to misclassification of epilepsy subtypes. Adherence was based on the available clinical documentation and was not independently quantified.

Conclusion

The prevalence of refractory epilepsy observed in this study 19.4% falls at the lower end of the commonly reported global range.

Recommendations: Future research should focus on multicenter, large-scale, and more demographically diverse cohort studies to enhance the generalizability of findings. The integration of genetic analyses and advanced functional imaging techniques may provide deeper insights into the mechanisms underlying drug resistance. Investigations aimed at improving treatment adherence, including direct monitoring of adherence, are also warranted. Furthermore, longitudinal studies are essential to evaluate long-term outcomes, encompassing seizure control, cognitive trajectories, and overall quality of life in patients with drug-resistant epilepsy.

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