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Drug-resistant epilepsy in Saudi Arabia: prevalence, predictive factors, and treatment outcomes

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Abstract

Background/Objectives Drug-resistant epilepsy (DRE) is a significant global public health challenge affecting people with epilepsy (PWE). Despite the availability of multiple drug therapies, a significant number of PWE with DRE continue to experience frequent seizures. Current data on the prevalence of DRE and associated risk factors in the Saudi population is limited. This study aimed to estimate and characterize DRE among PWE and identify associated predictive factors.

Materials and methods A cross-sectional study was conducted on PWE who attended Neurology clinics at the National Guard Health Affairs in Riyadh, Saudi Arabia (NGHA-R) between June 2016 and February 2023. Data were collected from patient medical records. Descriptive analyses of continuous and categorical variables were performed. Comparisons between categorical data were conducted using Pearson's chi-squared test. Multivariable logistic regression was used to identify independent factors associated with the development of DRE. A p-value of < 0.05 was considered statistically significant.

Results A total of 350 patients were analyzed, with a confirmed DRE prevalence of 26.86% (94 out of 350). Age-specific analysis revealed that DRE was most prevalent in the 29–39 age group, accounting for 35.1% (33 out of 94) of cases. The primary predictor for DRE was focal seizure type (AOR = 1.85; 95% CI: 1.05–3.27, $p = 0.03$). Additionally, DRE patients were more likely to visit the emergency room. Among antiseizure medications, treatment regimens of valproic acid ($p = 0.0008$), carbamazepine ($p = 0.0097$), and lamotrigine ($p = 0.037$) showed significant associations with DRE status.

Conclusion The prevalence of DRE in Saudi Arabia remains within the previously reported range of global prevalence. Frequent emergency department visits and the use of ASM polytherapy should be followed up closely to ensure early diagnosis of DRE and improve clinical outcomes.

Keywords ASMs, Drug-resistant epilepsy, Prevalence

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Introduction

Epilepsy is defined by the International League Against Epilepsy (ILAE) as a primarily clinical diagnosis characterized by either two or more unprovoked seizures occurring at least 24 h apart, or a single unprovoked seizure with a risk of recurrence higher than that of the general population [1]. Seizures occur through excessive and abnormal synchronous electrical activity of neurons in the brain, leading to transient signs and symptoms [1]. They can be categorized as provoked, resulting from identifiable causes, or unprovoked, with no apparent trigger [2]. The classification of seizures is based on the origin of the abnormal electrical activity. Focal seizures, previously known as partial seizures, are restricted to one hemisphere of the brain, whereas generalized seizures involve both hemispheres [3]. According to the World Health Organization (WHO), epilepsy affects over 50 million people globally [4]. In Saudi Arabia, the incidence of active epilepsy is estimated at 3 to 5 per 1,000 individuals [5]. Among the various seizure types, focal seizures with impaired awareness are the most common (33%), followed by generalized seizures (29.1%) [5].

Epilepsy is effectively controlled in 70–80% of patients through anti-seizure medications (ASMs) [6]. However, a subset of patients does not achieve satisfactory seizure control despite treatment. To standardize definitions and avoid ambiguity, the ILAE defines drug-resistant epilepsy (DRE) as the failure to achieve sustained seizure freedom despite adequate trials of two well-tolerated and appropriately chosen ASM regimens, whether as monotherapy or combination polytherapy [7].

Globally, DRE is estimated to affect 30–40% of people with epilepsy (PWE) [8, 9]. In Saudi Arabia, a retrospective cohort study conducted in Al-Khobar reported a 30% prevalence of DRE among individuals diagnosed with epilepsy [10]. However, that study was conducted over two years and focused exclusively on patients aged 14 years and older. Our study takes a broader approach, including pediatric and adult patients, to provide a more comprehensive picture of DRE prevalence. Conducted over a longer timeframe, from 2016 to 2023, our research captures a larger and more diverse dataset, offering deeper insights into patient demographics and clinical characteristics.

Accumulating evidence highlights several factors that increase the risk of developing DRE, resulting in a substantially higher healthcare burden compared to well-controlled epilepsy. These include early age of onset, symptomatic epilepsy, neurological deficits, neuroinflammation, non-response to the first prescribed ASM, and episodes of status epilepticus [11, 12]. Moreover, patients with DRE experience higher rates of hospitalization, often for surgeries or post-seizure monitoring, and more frequent emergency room visits due to breakthrough seizures [13, 14, 15]. Previous studies have established a strong association between frequent emergency room visits and the use of polytherapy ASM regimens in patients with DRE [15, 16].

Polytherapy is considered a viable approach for managing DRE [17]; however, longitudinal studies indicate that the likelihood of achieving a significant reduction in seizure frequency or seizure freedom diminishes with each additional ASM regimen attempted [18, 19]. Consequently, prioritizing ASMs with greater demonstrated efficacy early in treatment may improve outcomes for DRE patients.

There is a paucity of data on the prevalence of DRE in Riyadh, Saudi Arabia. This is partly due to the fragmented nature of existing data collected from various locations and healthcare settings, making it challenging to establish an accurate picture of the regional incidence of DRE. To address this gap, we conducted a comprehensive cross-sectional study focusing on PWE treated at a single medical center in Riyadh. Our objective was to estimate the prevalence of DRE in the central region of Saudi Arabia and provide valuable insights into this critical public health issue.

Methodology

Study design and participants

This hospital-based cross-sectional study was conducted from June 2016 to February 2023 at the NGHA-R, a tertiary governmental, academic hospital that serves a large population in the central region of Saudi Arabia and receives referrals from eleven primary healthcare centers. NGHA-R neurology clinic serves approximately more than 4000 patients per year.

Data were collected from the electronic medical records of patients with confirmed epilepsy diagnoses in the BESTCare 2.0 system at King Abdullah Medical City (KAMC), Riyadh, Saudi Arabia. KAMC manages more than 4000 epileptic outpatients every year. A sample size of 323 patients was required to estimate a 30% prevalence rate of DRE with 95% confidence and a precision of 5%. A total of 350 epilepsy patients were included to enhance the study's representativeness. A random sampling method was employed to select patients' medical record numbers (MRNs). **Inclusion and exclusion criteria** Participants included patients previously diagnosed with epilepsy by neurology consultants regardless of age, age at diagnosis, type, and etiology of epilepsy, or current epilepsy status. Exclusion criteria were applied to patients with insufficient data for proper analysis, including incomplete documentation or insufficient follow-up visits.

Drug response classification

The study followed the ILAE guidelines for defining DRE [7]. Each patient's response to individual ASMs was evaluated to classify treatment outcomes. Each patient's response to individual ASMs was evaluated to classify treatment outcomes. Patients were categorized as responsive, DRE, or undefined. DRE was defined as failing to achieve sustained seizure freedom despite adequate trials of at least two appropriately chosen and tolerated ASMs administered at sufficient dosages and duration and prescribed to stop or control the seizures for at least 12 months. We consider a patient to be "undefined" if he/she has inadequate or insufficient dosage or poor compliance based on the patient's medical history and consistent neurological evaluations. All cases that fulfilled the criteria for DRE were reviewed with neurologists and the Principal Investigator to make sure there was adequate information needed to reach such a conclusion.

Ethical consideration

Ethical approval was obtained from the King Abdullah International Medical Research Center (KAIMRC) Institutional Review Board (NRC23R/221/04). Data collection adhered to relevant guidelines and regulations. Patient confidentiality was safeguarded, with all data stored in an encrypted Excel file accessible only to the research team. Due to the retrospective nature of the study, the requirement for informed patient consent was waived.

Data collection

Data were extracted for 350 patients using MRNs from the BESTCare 2.0 system and entered into a secure, protected Excel sheet. Collected variables included demographic data (age, gender), time since diagnosis, etiology, seizure type, emergency department visits due to seizures, and type of therapy. The classification of seizures and determination of etiology were conducted based on patient history, physical examination, and clinical findings under the supervision of neurology consultants.

Statistical analysis

Data analysis was performed using SPSS version 25.0. Descriptive statistics were computed, with frequencies used for categorical variables. Comparisons between categorical data were conducted using the chi-square test. multivariate logistic regression analyses were employed to identify associated factors of DRE. Statistical significance was defined as $P < 0.05$.

Results

Baseline characteristics of the study participants

A total of 350 patients were included in the study. Of these, 24 (6.8%) were under 18 years old, 117 (33.4%) were aged 18–28, 102 (29.2%) were aged 29–39, 45 (12.8%) were aged 40–50, and 62 (17.7%) were over 50 years old. Males comprised 53.1% (186) and females 46.9% (164) of the sample. Regarding the time since diagnosis, 79 (22.6%) had been diagnosed within the last five years, 112 (32.0%) between five and ten years ago, 42 (12.0%) between 11 and 15 years ago, 43 (12.3%) between 16 and 20 years ago, and 58 (16.6%) more than 20 years ago. For 16 (4.6%) participants, the diagnosis period was unknown.

The most common etiology was genetic and presumed genetic (66.3%, 232 cases), followed by structural causes (27.4%, 96 cases), infections (2.9%, 10 cases), and unknown causes (3.4%, 12 cases). Regarding epilepsy types, 43.1% (168) had focal epilepsy, 42.9% (150) had generalized, and 9.1% [32] had combined types. Among the DRE and undefined cases, 74.6% (97) experienced monthly seizures, 15.3% [20] reported no seizures, and 10.1% [13] had an unknown seizure status.

Emergency department visits due to seizures were reported by 28.6% (100) of patients, while 71.4% (250) had not sought urgent care. 243 (69.4%) patients were treated with monotherapy, while 107 (30.6%) patients received polytherapy (Table 1).

Prevalence of DRE

The confirmed prevalence of DRE was 26.86% (94 out of 350), while responsive was observed in 223 cases (63.71%); 33 cases (9.43%) were classified as undefined epilepsy (Fig. 1). Our analysis of age-specific prevalence indicates that DRE is notably more prevalent in the 29–39 age group, with a prevalence of 35.1% (33 out of 94). (Fig. 2)

Factors associated with epilepsy status

There was no significant difference across the epilepsy statuses in terms of age or gender. However, the approximate number of years since diagnosis was significantly associated with epilepsy status ($p = 0.002$). DRE was more common in participants who had been diagnosed between five and ten years ago. Etiology and type of seizure were also significantly associated with epilepsy status ($p = 0.001$ and $p = 0.005$, respectively). Infection-derived epilepsy was more likely to trigger seizures in the DRE group compared to non-DRE and undefined patients, and DRE was more commonly associated with a combination of seizure types. Emergency department visits due to seizures and therapy type were significantly associated with epilepsy status ($p < 0.001$ and $p < 0.001$, respectively). DRE patients were more likely to visit the emergency room (Table 2). On further multivariate regression analysis, focal seizure type (AOR = 1.85; (CI95%1.05–3.27) was found to be a predictor of DRE (Table 3).

Table 1 Baseline characteristics of the study participants

Characteristics	Overall
	Number (%)
Age (year)	
< 18	24 (6.8%)
18–28	117 (33.4%)
29–39	102 (29.2%)
40–50	45 (12.9%)
> 50	62 (17.7%)
Gender	
Male	186 (53.1%)
Female	164 (46.9%)
Approximate Number of Years Since the Diagnosis	
Less than 5	79 (22.6%)
Between 5 and 10	112 (32.0%)
Between 11 and 15	42 (12.0%)
Between 16 and 20	43 (12.3%)
More than 20	58 (16.6%)
Unknown	16 (4.6%)
Etiology	
Genetic and presumed genetic	232 (66.3%)
Structural	96 (27.4%)
Infection	10 (2.9%)
Unknown	12 (3.4%)
Epilepsy Type	
Focal	168 (43.1%)
Generalized	150 (42.9%)
Combined	32 (9.1%)
Seizure attack per month if DRE or Undefined	
Yes	97 (74.6%)
No	20 (15.3%)
Unknown	13 (10.1%)
Emergency Department Visit Due to Seizure	
Yes	100 (28.6%)
No	250 (71.4%)
Therapy type	
Monotherapy	243 (69.4%)
Polytherapy	107 (30.6%)

Distribution of ASM regimen

A chi-squared test was performed to examine the relationship between DRE status and ASM regimen (monotherapy vs. polytherapy). The relationship between these variables was significant for some ASMs, as shown in Table 4. Participants on a monotherapy regimen were more likely to have non-DRE compared to those on polytherapy, particularly in the cases of valproic acid ($p = 0.0008$) and carbamazepine ($p = 0.0097$). Similar trends were observed with lamotrigine and levetiracetam. However, for other ASMs, including topiramate, phenobarbital, and phenytoin, no significant differences were observed between monotherapy and polytherapy patients, likely due to a small number of patients.

Persistence of treatment

Among PWE, treatment persistence varied between groups. A vast majority of non-DRE patients, 150 continued with their previous line of treatment, compared to only 5 of DRE patients. These findings indicate that non-DRE patients typically perceive their treatment as effective. More than half of non-DRE patients, 104, opted to change their treatment, while 68 of DRE patients switched. Furthermore, 2 of non-DRE patients had their treatment augmented, whereas 21 of DRE patients required treatment augmentation to achieve a favorable response. (Fig. 3)

Discussion

Our data suggests a prevalence of DRE in Riyadh, Saudi Arabia of 27%. This estimate aligns closely with previous findings from Alshurem et al. in Alkhobar, Saudi Arabia, and the global prevalence of 30% reported by Kalilani et al. [10, 11]. A comprehensive systematic review and meta-analysis of 16 studies, including adults and children, also reported a prevalence of approximately 27% [12]. However, other studies report varying prevalence rates. For instance, a systematic review of 19 studies estimated a DRE prevalence of 20% but significant heterogeneity in the data, with reported rates ranging from 6 to 51% [12]. Another meta-analysis of 15 studies estimated a prevalence of 25% [11]. Higher rates have been reported in certain regions, such as Italy, where Gilio et al. reported a prevalence of 50.9% for medically refractory epilepsy [20], and Spain, where Villanueva et al. observed a prevalence of 70% [21]. These discrepancies could stem from differences in DRE definitions, genetic or ethnic predispositions, or the type of epilepsy studied.

In our study, the 29–39 age group demonstrated the highest DRE prevalence at 35.1%. This is consistent with a previous study of 410 patients, which found DRE to be predominant in the 20–39 age group [22]. A study from Singapore also reported DRE prevalence as highest in individuals aged 30–39 and 40–49, with lower prevalence in other age groups [23]. The variation in prevalence among older populations may relate to underlying pathogenesis and concurrent illnesses affecting health outcomes in these individuals.

To our knowledge, this study is the first to assess the prevalence of DRE in the central Saudi Arabian population, including both pediatric and adult patients. Our findings highlight the importance of several factors associated with DRE, including the number of years since diagnosis, etiology, seizure type, emergency department visits, and therapy type. However, we found no significant association between DRE and variables such as age and gender, consistent with the findings of Farghaly et al. in a study of 437 epilepsy patients [24].

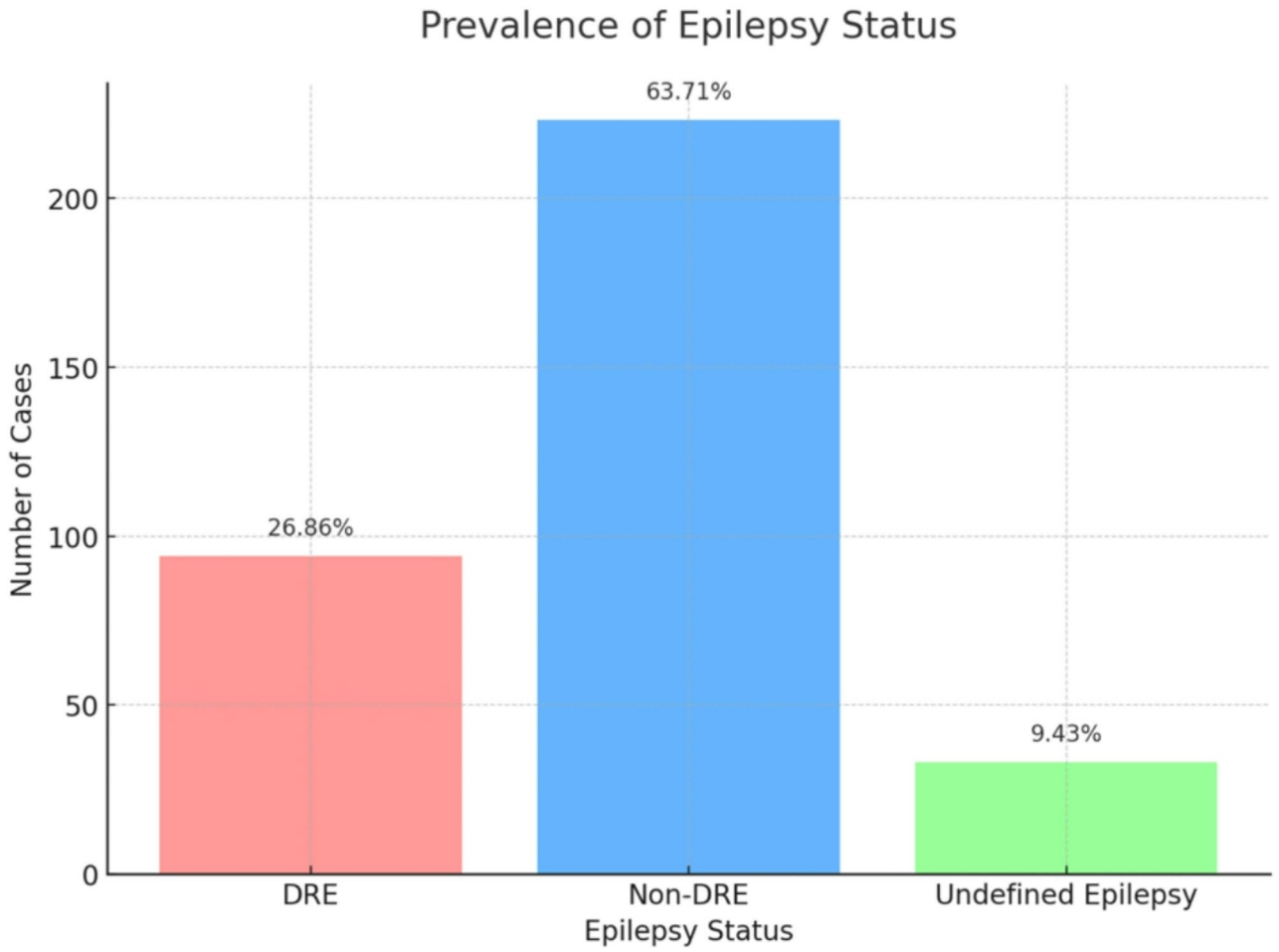

Fig. 1 Prevalence epilepsy status

Our results reveal genetic and presumed genetic factors as the most common etiology among epilepsy types, followed by structural causes. Prior studies in Saudi Arabia have also highlighted a notable increase in genetic mutations within the local population, with consanguineous marriage recognized as a significant risk factor [25]. For instance, 13% of early childhood epilepsy in Saudi Arabia is attributed to genetic causes [26, 27]. Bashiri et al. identified six genetic mutations in children with epilepsy at a single Saudi center between 2015 and 2018 [26]. Recently, a retrospective study conducted at King Saud Medical City found that epilepsy was the primary reason for molecular genetic investigations, accounting for 309 cases (35.7%) between September 2020 and December 2021 [28]. The predominance of genetic etiology may be attributed to cultural and socio-economic factors, highlighting the need for further studies to address and mitigate genetic disorders effectively.

Infections were found to be more prevalent in the DRE group, despite their low overall incidence. Neuroinflammation has been implicated in disrupting the blood-brain barrier, initiating a cascade of signaling processes that may lead to DRE [29]. However, due to the small sample size of infection cases among PWE, further population-based research is needed to validate these findings.

Seizure type was significantly associated with DRE, with partial/focal epilepsy showing increased prevalence in this population, consistent with other studies [24, 30, 31]. Combined seizures were also more common in the DRE group.

Emergency department visits and therapy type were independently linked to seizure type. This likely reflects the frequency and severity of seizures in patients with DRE, which often require urgent medical attention. A recent study investigated seizure burden and healthcare resource utilization among individuals with DRE focal epilepsy in the United States; 43% of patients experienced emergency department visits and 24% were hospitalized, primarily due to breakthrough seizures [32]. These findings are comparable to our data, in which 65 patients (47.79%) required emergency care. The slightly higher

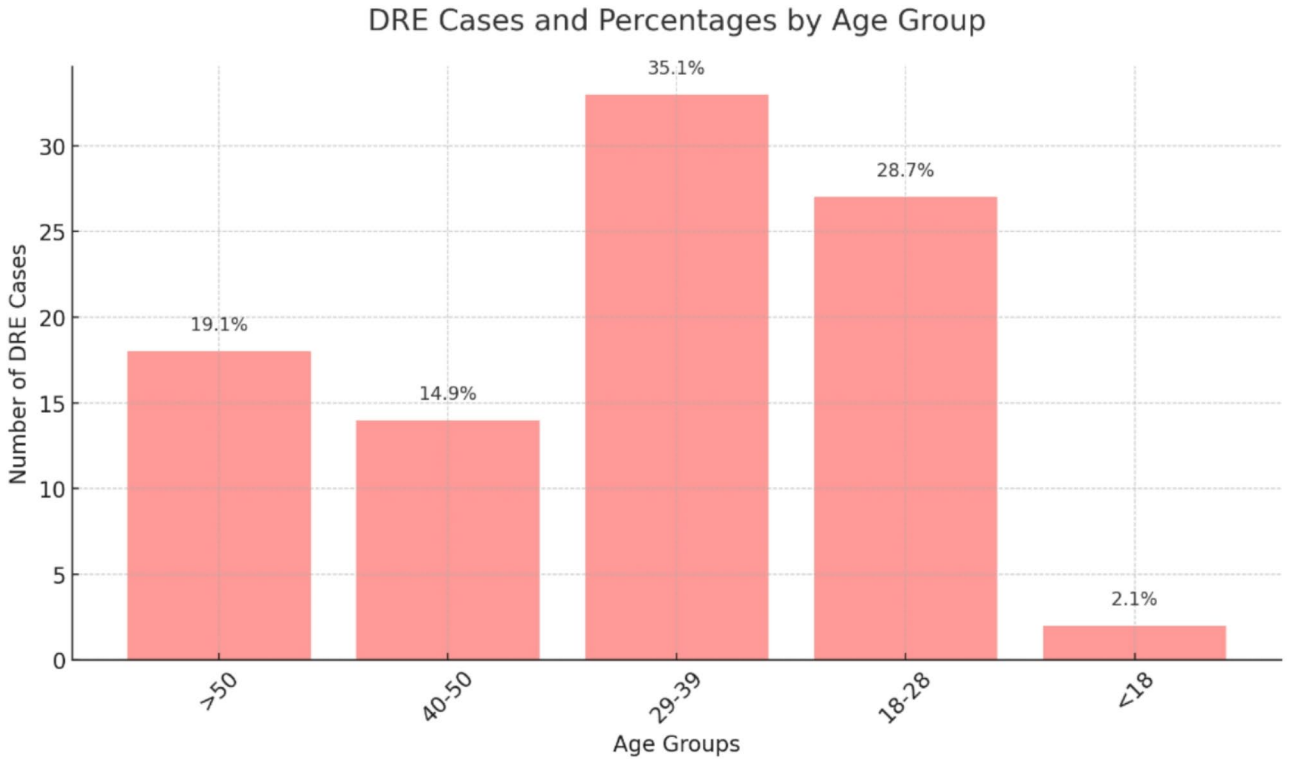

Fig. 2 DRE cases among age groups

rate in our study may be attributable to the inclusion of both focal and generalized seizure types.

The persistence of 39 (15.9%) DRE patients on monotherapy highlights a crucial aspect of epilepsy management—balancing seizure control with treatment-related adverse effects and overall quality of life. A retrospective study conducted in the United States between January 2013 and January 2020 found that 32.5% of DRE patients were on third-line monotherapy, while 11.2% were on fourth-line monotherapy [33]. These findings align with our data, suggesting that, despite previous treatment failures, some clinicians and patients continue to prefer monotherapy over polytherapy. Second- and third-generation ASMs have improved the treatment options and outcomes for epilepsy. However, rates of drug resistance have remained consistent, likely due to the complex and poorly understood etiology of resistance. Previous studies have linked polytherapy with increased emergency visits [12]. Moreover, accumulating evidence shows that the efficacy of ASMs significantly declines with each additional line of therapy [18, 32], underscoring the importance of considering combined treatment only after monotherapy failure.

Previous work by Can et al. (2020) reports levetiracetam, valproate, and lamotrigine as the most used ASMs among their study population. In the current study, levetiracetam, valproate, and carbamazepine were the most common. In our study, the association between the treatment regimen and ASMs was significant for valproic acid, carbamazepine, and lamotrigine.

Our study revealed that most DRE patients had either switched or augmented their treatment to its present form. Although we could not determine the duration of each therapy, it is tempting to speculate that most DRE patients who switched therapy had experienced side effects or displayed poor adherence due to dosage frequency. Conversely, patients with DRE who opted for augmentation may have experienced partial improvement with their prior treatment regimen.

The primary limitation of this study lies in its cross-sectional design and focus on a single hospital in Riyadh, restricting generalizability to other populations. Given the country's geographical variability, major differences in DRE prevalence likely exist between urban and rural areas. Nonetheless, these findings may be applicable to hospital-based epilepsy patients in regions with socio-demographics similar to Riyadh. Future multi-center and population-based studies are needed to provide a comprehensive understanding of DRE in Saudi Arabia.

Conclusion

This report introduces a study estimating the prevalence of DRE in Riyadh, Saudi Arabia, for the first time. It indicates that the prevalence rates in this population are consistent with those reported in other regions. Results regarding predictive factors associated with DRE

Table 2 Baseline characteristics of patients

Characteristics	Epilepsy status (%)			*p*-value
	Responsive	DRE	Undefined	
Age				
> 18	9 (64.3)	2 (14.3)	3 (21.4)	0.073
18–28	82 (64.6)	27 (21.3)	18 (14.2)	
29–39	64 (62.7)	33 (32.4)	5 (4.9)	
40–50	26 (57.8)	14 (31.1)	5 (11.1)	
> 50	42 (67.7)	18 (29.0)	2 (3.2)	
Gender				
Male	116 (62.4)	52 (28.0)	18 (9.7)	0.8529
Female	107 (65.2)	42 (25.6)	15 (9.1)	
Approximate Number of Years Since the Diagnosis				
Less than 5	47 (59.5)	15 (19.0)	17 (21.5)	**0.002**
Between 5 and 10	77 (68.8)	29 (25.9)	6 (5.4)	
Between 11 and 15	31 (73.8)	10 (23.8)	1 (2.4)	
Between 16 and 20	29 (67.4)	11 (25.6)	3 (7.0)	
More than 20	11 (26.8)	25 (61.0)	5 (12.2)	
Unknown	16 (76.2)	4 (19.0)	1 (4.8)	
Etiology				
Genetic and presumed genetic	156 (67.2)	55 (23.7)	21 (9.1)	**< 0.001**
Structural	63 (65.6)	30 (31.2)	3 (3.1)	
Infection	2 (20.0)	7 (70.0)	1 (10.0)	
Unknown	2 (16.7)	2 (16.7)	8 (66.7)	
Type of Seizure				
Focal	110 (62.9)	52 (29.7)	13 (7.4)	**0.005**
Generalized	101 (70.6)	28 (19.6)	14 (9.8)	
Combined	12 (37.5)	14 (43.8)	6 (18.8)	
Emergency department visit due to seizure				
Yes	61 (44.9)	65 (47.8)	10 (7.4)	**< 0.001**
No	162 (75.7)	29 (13.6)	23 (10.7)	
Therapy type				
Monotherapy	195 (79.3)	39 (15.9)	12 (4.9)	**< 0.001**
Polytherapy	28 (26.9)	55 (52.9)	21 (20.2)	

Table 3 Factors associated with DRE among PWE

Predictive factors	Category	DRE (%)		AOR (95% CI)	*p*-value
		No	Yes		
Age (Years)	< 18 Pediatric	12 (85.7)	2 (14.2)	2.65 (0.41–17.12)	0.31
	> 18 adults	244 (72.6)	92 (27.3)		
Gender	Male	134 (72.0)	52 (27.9)	1.05 (0.61–1.83)	0.85
	Female	122(74.3)	42 (25.6)		
Approximate Number of Years Since the Diagnosis	between 5–10	83 (74.1)	29 (25.8)	1.03 (0.56–1.89)	0.93
	< 5 - >10	173 (72.6)	65 (27.3)		
Etiology	Genetic and presumed genetic	177 (76.2)	55 (23.7)	0.72 (0.41–1.29)	0.27
	Non– Genetic and presumed genetic	79 (66.9)	39 (33.1)		
Seizure Type	Focal	123 (70.2)	52 (29.7)	1.85 (1.05–3.27)	**0.03***
	Non - Focal	133 (76)	42 (24)		

highlight the importance of close follow-up to patients' emergency room visits and treatment plans. We also recommend further research into the genetic factors influencing DRE, as such studies could provide valuable insights into the underlying causes of this condition.

To gain a more comprehensive understanding of the relationship between epilepsy status and ASM response, additional investigations are necessary. Such research would benefit from larger sample sizes, and the examination of various factors, such as gene polymorphisms and co-morbidities.

The findings from these investigations will be instrumental in enabling the implementation of effective

Table 4 The effect of the ASM regimen on DRE status among PWE

ASM	Regimen	DRE (%)		AOR (95% CI)	*p*-Value
		No	Yes		
Levetiracetam (*N* = 164)	Monotherapy (*N* = 105)	86 (81.9)	19 (18.0)	0.71 (0.33,1.55)	0.51
	Polytherapy (*N* = 59)	45 (76.2)	14 (23.7)		
Carbamazepine (*N* = 93)	Monotherapy (*N* = 62)	54 (87.0)	8 (12.9)	0.23 (0.08,0.066)	**0.0097***
	Polytherapy (*N* = 31)	19 (61.2)	12 (38.7)		
Valproic acid (*N* = 49)	Monotherapy (*N* = 32)	30 (93.7)	2 (6.2)	0.059 (001.033)	**0.0008***
	Polytherapy (*N* = 17)	8 (47.0)	9 (52.9)		
Lamotrigine (*N* = 37)	Monotherapy (*N* = 23)	16 (69.5)	7 (30.4)	0.17 (0.04,0.75)	**0.037***
	Polytherapy (*N* = 14)	4 (28.5)	10 (71.4)		
Phenobarbital (*N* = 16)	Monotherapy (*N* = 5)	4 (80.0)	1 (20.0)	0.66 (0.05,8.64)	1.00
	Polytherapy (*N* = 11)	8 (72.7)	3 (27.2)		
Phenytoin (*N* = 12)	Monotherapy (*N* = 7)	6 (85.7)	1(14.2)	0.66 (0.03, 14.04)	1.00
	Polytherapy (*N* = 5)	4(80.0)	1(20.0)		
Topiramate (*N* = 7)	Monotherapy (*N* = 2)	1(50.0)	1(50.0)	2.0 (0.08,51.60)	1.00
	Polytherapy (*N* = 6)	4 (66.6)	2 (33.3)		
Lacosamide (*N* = 4)	Monotherapy (*N* = 3)	3(100)	0	NA	0.50
	Polytherapy (*N* = 1)	0	1(100)		
Others (*N* = 11)	Monotherapy (*N* = 6)	6(100)	0	NA	0.12
	Polytherapy (*N* = 5)	2(40.0)	3(60.0)		

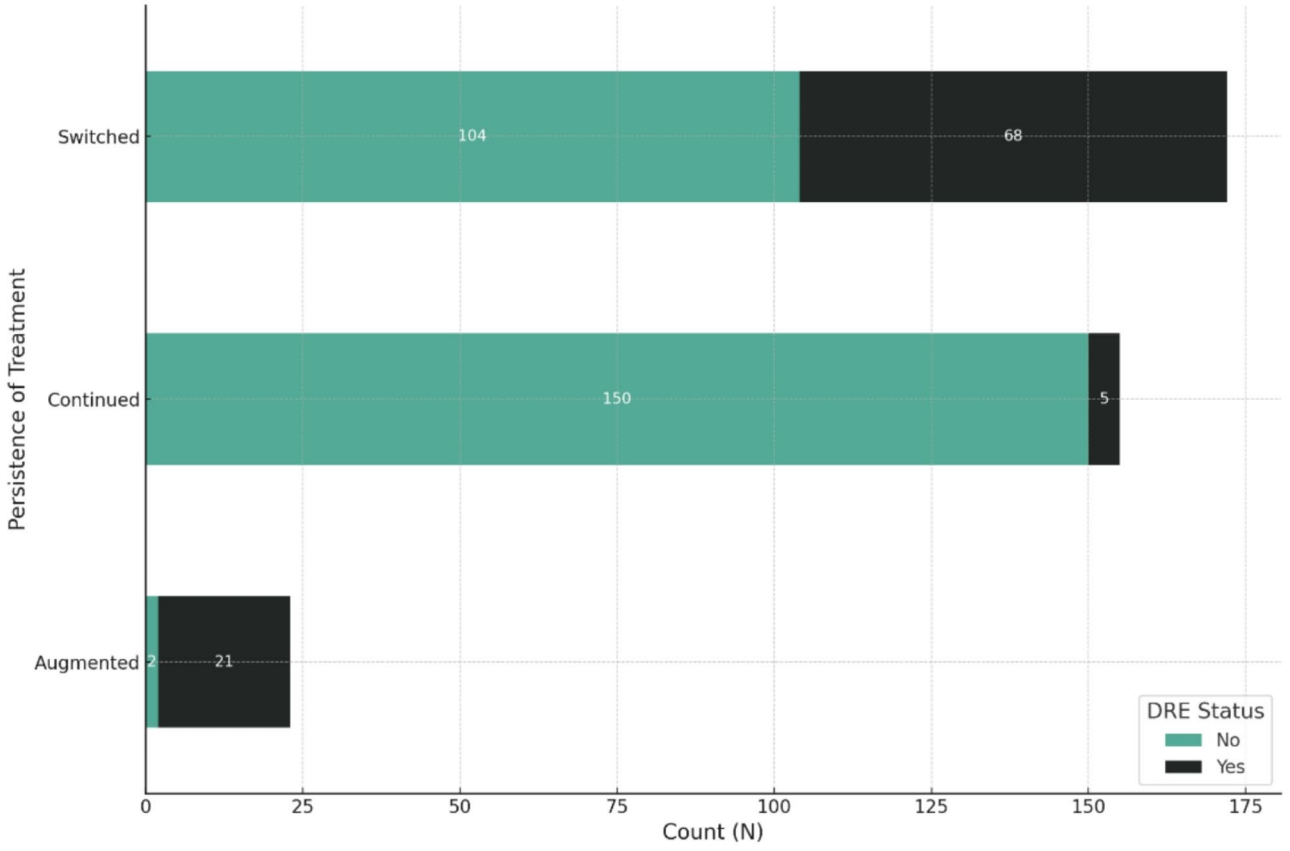

Fig. 3 Distribution of PWE among treatment status

treatment guidelines and the more strategic allocation of resources to better support DRE.

Author contributions
MA: study conceptualization, data collection, literature research. NA: manuscript drafting/finalization, literature research. NA: Figures. RG, AFA, and RN: data collection, literature research. SA: supervision and manuscript review.

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Data availability
The authors confirm that the data supporting the findings of this study are available within the article. The raw data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the King Abdullah International Medical Research Center (KAIMRC) Institutional Review Board (IRB) (NRC23R/221/04). This research was carried out in accordance with the Declaration of Helsinki. Waiver of written informed consent was approved by the IRB due to the retrospective design of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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