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A scale for prediction of response to AEDs in patients with MRI-negative epilepsy

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ABSTRACT

Objectives: Antiepileptic drugs (AEDs) are the first choice in magnetic resonance imaging (MRI)-negative patients with epilepsy, although the responses to AEDs are diverse. Preoperative evaluation and postoperative prognosis in MRI-negative epilepsy have been reported. However, there are few tools for predicting the response to AEDs. Herein, we developed an AED response scale based on clinical factors and video-electroencephalography (VEEG) in MRI-negative patients with epilepsy.

Methods: A total of 132 consecutive patients with MRI-negative epilepsy at the Epilepsy Center of Henan Provincial People's Hospital between August 2016 and August 2018 were included. Patients were further divided into drug-responsive epilepsy ([DSE-MRI (−)]; n = 101) and drug-resistant epilepsy ([DRE-MRI (−)]; n = 31) groups. The clinical and VEEG factors were evaluated in univariate analyses and multivariate logistic regression analyses. A scale was derived and the scores categorized into 3 risk levels of DRE-MRI (−).

Results: A scale was established based on 4 independent risk factors for DRE-MRI (−). The scale had a sensitivity of 83.87%, specificity of 80.20%, positive likelihood ratio of 4.24, negative likelihood ratio of 0.20, and showed good discrimination with the area under the curve (AUC) of 0.886 (0.826–0.946). The categorization of the risk score based on this scale was: low risk (0–3 points), medium risk (3–5 points), and high risk (>5 points).

Conclusion: We established a DRE-MRI (−) scale with a good sensitivity and specificity, which may be useful for clinicians when making medical decisions in patients with MRI-negative epilepsy.

1. Introduction

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and epileptogenesis is the development of a neuronal network in which spontaneous seizures occur [1]. Antiepileptic drugs (AEDs), with an effectiveness of approximately 60%, are the first treatment choice for most patients with epilepsy [2]. Only 45.4% of patients with newly diagnosed epilepsy achieved seizure freedom at least 1 year after the first drug treatment, while >50% of patients must try 2 or more AEDs [3]. Further, 30%–40% of patients will develop drug-resistant epilepsy (DRE) [4]. Thus, it is extremely important to identify predictors associated with the response to AEDs. Several retrospective studies have found that early onset of epilepsy, higher frequency of seizures, multiple seizure types, prolonged disease duration, symptomatic etiology (such as hippocampal sclerosis), family history of epilepsy, perinatal history, initial precipitating injuries (IPIs), a poor response to the first AED trial, and some electroencephalographic features are associated with a poor response to AEDs [5–17].

Magnetic resonance imaging (MRI) has contributed to the elucidation of structural etiologies in epilepsy [18], such as tumors, gliosis/hippocampal sclerosis, malformations of cortical or vascular development, and other epileptogenic foci, along with the identification of treatment responders, assessment of patients' prognosis, and selection of suitable therapeutic options [19]. Accounting for 18%–43% of preoperative assessment, MRI-negative epilepsy is a huge surgical challenge because of the lack of a clear epileptogenic focus. Preoperative assessment is more complicated; surgical complications are more frequent, and the prognosis is worse than for patients with MRI-positive epilepsy. Further, identification of a structural lesion in patients with epilepsy indicates a poor chance of succeeding in seizure control with AEDs alone [20,21]. For MRI-negative epilepsy, the drug response is better than for epilepsy with structural lesions. Drug response in epilepsy is most likely an epiphenomenon that reflects the characteristics of the underlying epileptogenic process, which results from the complex interaction of genetic characteristics, underlying pathology, and environment

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[22]. Clinical features, electroencephalography (EEG), and imaging studies have helped to elucidate the complexity of AED responses.

Clinical prediction rules (CPRs) or scales (sometimes also called clinical decision rules) are used to predict DRE in children [23], and represent tools designed to assist in making medical decisions; CPRs can provide a probability of outcomes, or suggest a diagnostic or therapeutic course of action, and are usually created by multivariable logistic regression [24]. There are 4 phases for establishing a CPR: (1) development by identification of predictors, (2) validation, (3) impact analysis by measurement of cost–benefit and satisfaction, and (4) implementation [23,25]. In the present study, we developed a scale for responses to AEDs based on CPRs in patients with MRI-negative epilepsy.

2. Materials and methods

2.1. Study population

We retrospectively collected data from 536 patients with newly diagnosed MRI-negative epilepsy at the Epilepsy Center of Henan Provincial People's Hospital between August 2016 and August 2018 (Fig. 1). Inclusion criteria included the following: (i) presence of an epilepsy and/or epileptic seizures as defined by the guidelines of the International League Against Epilepsy (ILAE) [24,26], (ii) diagnosed with MRI-negative epilepsy [27], (iii) regular follow-up every 3 months, and (iv) video-EEG (VEEG) monitoring performed before AED. Exclusion criteria were as follows: (i) acute symptom onset, (ii) follow-up for <6 months [28,29], (iii) etiologic groups are genetic and metabolic, (iv) epileptic syndrome, (v) patient underwent epilepsy surgery, and (vi) poor compliance. Ultimately, 132 patients were included in our analysis. This study was approved by the Ethics Committee of Henan Provincial People's Hospital. All participants provided written informed consent.

The medical history included sex, age, age at seizure onset, pretreatment duration, seizure type, total seizure frequency before AED (pretreatment seizure frequency), seizure frequency for the previous 6 months before starting AED, febrile seizures, family history of epilepsy (when epilepsy was present in at least 1 first-degree relative), presence of initial precipitating injuries (IPIs), and VEEG and MRI findings. Comorbidity, such as anxiety and depression, were assessed with the Hamilton Anxiety Rating Scale and the Hamilton Depression Rating Scale, respectively. The choice of AED, period of titration, and initial maintenance dose were decided by the treating clinician, and the minimum effective dose of the drug was recommended. At the same time, we defined 'Drug-resistant epilepsy' as the failure of adequate trials of 2 tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [30].

Based on the last outpatient or telephone follow-up records, patients were classified as 'drug-responsive epilepsy [DSE-MRI (−)]' or 'drug-resistant epilepsy [DRE-MRI (−)]'.

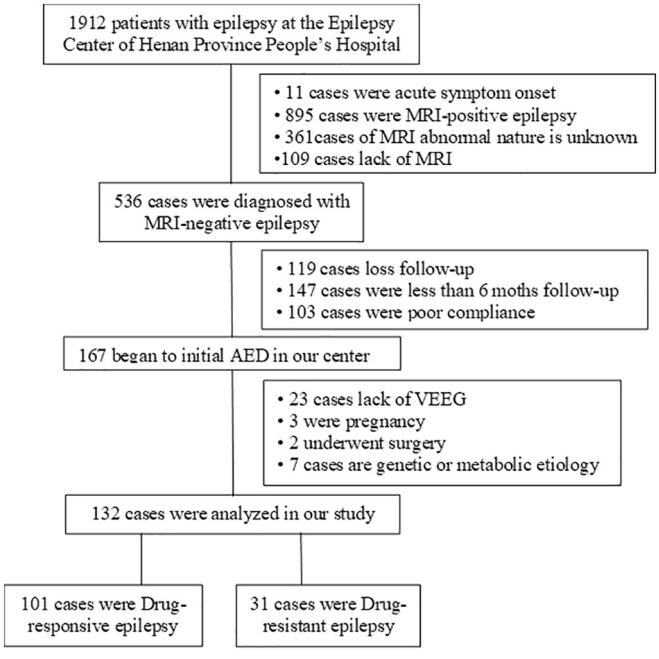

Fig. 1. Flow chart. VEEG: video-electroencephalography; AED: antiepileptic drug.

2.2. MRI

The MRI scans before AED corresponded to epilepsy MRI protocols for the detection of epileptogenic lesions described as follows [31,32]: MRI was performed on a 3.0-T unit (Siemens, Erlangen, Germany) with a conventional sagittal isotropic (1 mm) 3-dimensional T1-weighted gradient recalled echo (with 1-mm axial and coronal multiplanar reformations), axial fast spin echo T2-weighted (3- to 4-mm slice thickness at 3- to 4.5-mm intervals), axial T2 fluid-attenuated inversion recovery (FLAIR) (4-mm slice thickness at 4.5-mm intervals), coronal oblique T2 FLAIR (perpendicular to the plane of the hippocampus, 3- to 4-mm slice thickness at 3- to 4-mm intervals), and sagittal isotropic (1 mm) 3-dimensional T2 FLAIR (with 1-mm axial and coronal multiplanar reformations) sequences. All MRI images were analyzed by at least 2 experienced radiologists, who were blinded to the patients' clinical information. Discrepancies in judging the occurrence of abnormalities were settled by joint discussion of the 2 radiologists.

2.3. VEEG

Interictal scalp EEG was performed in all patients using a VEEG monitoring system, with electrodes placed according to the International 10–20 System and additional anterior temporal electrodes in a dark and quiet room. Scalp EEG was recorded over 10 h, including routine induction experiments, such as the open–close eyes test, hyperventilation, and intermittent photic stimulation. Each EEG was recorded digitally with a 256-Hz sampling rate (Nihon Kohden, Tokyo, Japan) Amplifier characteristics were 10,00 times gain, low-pass filter at 0.5 Hz, and high-pass filter at 70 Hz. All ictal VEEG recordings were analyzed by at least 2 experienced senior electroencephalographers. Controversies were settled by joint discussion of the 2 electroencephalographers.

2.4. Statistical analysis

All analyses were conducted using statistical software (IBM SPSS Statistics for Windows v.22.0; IBM Co., Armonk, NY, USA). Descriptive variables were expressed as median and quartile range, and categorical variables were expressed as frequencies and percentages. Normality tests showed that the continuous variables in our study were nonnormally distributed. Thus, the prognostic factors were evaluated by the Wilcoxon rank sum test for continuous variables. The chi-square or Fisher's exact test was performed for the comparison of categorical variables. Multivariate logistic regression was performed to assess the association between the predictor variables in patients with MRI-negative epilepsy. We used the stepwise probability to develop a multiple logistic regression model, of which the entry was 0.05, and removal was 0.10. The odds ratio and the 95% confidence interval were calculated.

To develop the predictive risk scale, we calculated the p-value of each prognostic factor that was kept with a p-value of <0.05. We then assigned a weight to the prognostic factors according to relative β coefficient. Next, we defined the normal VEEG as baseline; the highest p-values were assigned a score of 1, and the score of each prognostic

factor was calculated with the statistically significant p-values. Next, a receiver-operating characteristic curve analysis was used to calculate the sensitivity, specificity, and area under the curve (AUC) for the accuracy of the CPR. For categorization, the cutoff value was calculated by a maximum sum of the sensitivity and specificity. Finally, we calculated the possibility of DRE-MRI (−) using this scale. In all tests, a p-value <0.05 was considered statistically significant, unless otherwise stated.

3. Results

3.1. Demographics and baseline clinical characteristics

After exclusion criteria, 132 eligible patients were included in this study (Fig. 1). The detailed clinical and demographic characteristics are shown in Table 1. Of those enrolled, 101 (76.5%) were DSE-MRI (−), and 68 (51.5%) were male. The median age at seizure onset was 21 (quartile range: 13–30) years. The median pretreatment duration of epilepsy was 16.5 (quartile range: 7–36) months. The median number of seizures before AED was 5 (quartile range: 3–14.75).

3.2. Possible risk factors for DRE-MRI (−)

There were 8 risk factors related to the response to AED in univariate analysis (Table 2), including longer duration of epilepsy, higher number of seizures before AED, higher seizure frequency before AED, seizure type, poor response to the first AED, comorbidities, abnormal VEEG before AED, and >1 recurrence in the first 6 months after diagnosis, which were all related to poor response to AEDs. In multivariate analysis, there were 4 independent risk factors for DRE-MRI (−), including abnormal EEG, history of central nervous system (CNS) infection, the presence of IPIs, and >1 recurrence in the first 6 months after diagnosis (Table 3).

3.3. Derivation of a scale

We developed a scale based on the multivariable logistic regression (Table 3). The scale showed a good discrimination, with an AUC of 0.886 (0.826–0.946; Fig. 2). For each β coefficient, a weight was assigned to each risk factor. By adding up the weight, individual DRE-MRI (−) risk scores were given to each predictive factor, ranging from 0 to 2. The overall sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of this scale were 83.87%, 80.20%, 4.24, and 0.20 (Table 4), respectively. Based on the sensitivity and specificity, the best cutoff point for the score was 3 points (Fig. 2). The risk level was categorized as low risk (0–3 points), medium risk (3–5 points), and high risk (>5 points). The probability of DRE-MRI (−) based on the score was shown in Table 5, with 2.62%–34.19% in the low risk level, 34.19%–90.00% in the medium risk level, and >90.00% in the high risk level.

Table 1
Clinical and demographic characteristics of MRI-negative epilepsy (n = 132).

Variables	N (%)/(median, quartile range)
Male	82(62.12%)
Age, (years)	21(13–30)
Age at onset, (years)	17(11–25)
Duration of epilepsy, (months)	16.5(7–36)
Seizure times before AED, (times)	5(3–14.75)
Presence of IPIs	13(9.85%)
Generalized onset	60(45.45%)
VEEG Epileptiform before AED	70(53.03%)
The response to the first AED	66(50.00%)
Presence of comorbidities	31(23.48%)
More than one recurrence in the first six months after diagnosis	54(40.91%)

MRI: magnetic resonance imaging; AED: antiepileptic drug; VEEG: video-electroencephalography; IPIs: initial precipitating injuries.

Table 2
The possible risk factors of DRE-MRI (−).

Variable	DSE N = 101(%)	DRE N = 31(%)	χ2/Z	p value
Sex				
Male	62(61.39)	20(64.52)	0.099	0.753
Female	39(38.61)	11(35.48)		
Age, (years)	18(12–29)	26(17–32)	−1.856	0.063
Age at onset, (years)	15(11–26)	19(10–25)	−0.287	0.774
Duration of epilepsy, (months)	12(5.5–26)	70(23–96)	−5.693	<0.001
Seizure times before AED, (times)	4(2.5–6.5)	45(20–95)	−7.728	<0.001
Seizure frequency before AED, (times/months)	0.3(0.2–0.7)	1(0.4–2.0)	−3.652	<0.0001
Seizure type				
Generalized	50(49.50)	10(32.26)		
Focal	31(30.69)	7(22.58)	8.017	0.018
Combined two types	20(19.81)	14(45.16)		
The response to the first AED				
Yes	66(65.35)	0(0.00)	40.515	<0.001
No	35(34.65)	31(100.00)		
Comorbidities				
Yes	19(18.81)	12(38.71)	5.226	0.022
No	82(81.19)	19(61.29)		
Perinatal history				
Yes	12(11.88)	5(16.13)	0.097	0.756
No	89(88.12)	26(83.87)		
Family history of epilepsy				
Yes	13(12.87)	5(16.13)	0.027	0.870
No	88(77.19)	26(83.87)		
History of CNS infection				
Yes	10(9.90)	7(22.58)	2.363	0.124
No	91(90.10)	24(77.42)		
Febrile seizures				
Yes	15(14.85)	4(12.90)	0.073	0.787
No	86(85.15)	27(87.10)		
Initial precipitating injuries				
Yes	8(7.92)	5(16.13)	0.994	0.319
No	93(92.08)	26(83.87)		
VEEG before AED				
Normal	44(43.56)	5(16.13)		
Epileptiform	48(47.53)	22(70.97)	8.145	0.004
Not epileptiform	9(8.91)	4(12.90)		
More than one recurrence in the first six months after diagnosis				
Yes	28(27.72)	26(83.87)	30.934	<0.001
No	73(72.28)	5(16.13)		

DSE: drug-responsive epilepsy; DRE: drug-resistant epilepsy; MRI: magnetic resonance imaging; AED: antiepileptic drug; VEEG: video-electroencephalography; CNS: central nervous system.

4. Discussion

4.1. Definition of MRI-negative epilepsy

Despite a number of reports on MRI-negative epilepsy, there remains no clear definition by the ILAE. A few studies have used the terminology of 'normal MRI'. In clinical practice, we often find some abnormalities that do not cause seizures using a conventional MRI protocol,

Table 3
The risk factors of DRE-MRI (−) and its score derivation.

	OR (95%CI)	B-coefficient	p value	Score
Normal VEEG (baseline)	1			0
Epileptiform	7.129(1.931–26.318)	1.964	0.003	1.5
Not epileptiform	13.877(1.758–109.525)	2.630	0.013	2
History of CNS infection	3.940(0.994–15.617)	1.371	0.051	1
Initial precipitating injuries	7.135(1.366–37.260)	1.965	0.020	1.5
More than one recurrence in the first six months after diagnosis	23.234(6.552–82.395)	3.146	<0.001	2

DRE: drug-resistant epilepsy; MRI: magnetic resonance imaging; VEEG: video-electroencephalography; CNS: central nervous system; OR: odds ratio; 95%CI: 95% confidence interval.

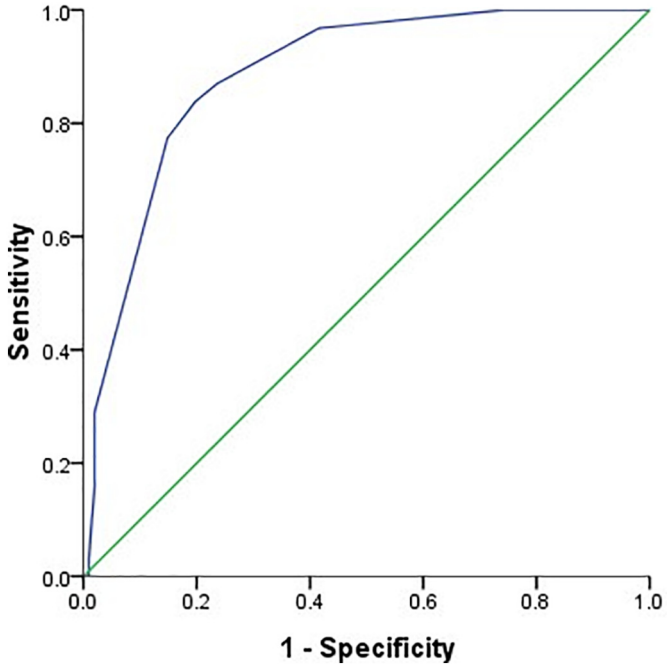

Fig. 2. Accuracy of DRE-MRI (−) prediction by scoring explained by AUROC curve 0.886 (0.826–0.946). DRE: drug-resistant epilepsy; AUROC: area under the curve of receiver-operating characteristic.

which include cerebral atrophy and nonspecific abnormal white matter signals. However, these cannot be considered a normal MRI. 'Nonlesional MRI' is another terminology used for MRI-negative epilepsy. However, >50% of surgical specimens in nonlesional MRI were found to exhibit pathological changes, including single ganglioma and focal cortical dysplasia [33]. In the present study, we defined 'MRI-negative' as the absence of abnormalities, or the presence of lesional or structural abnormalities that did not directly cause epilepsy and/or seizures. These lesional or structural abnormalities include brain atrophy, nonspecific abnormal white matter signals, and mild asymmetry in the size and shape of certain brain regions [27]. This definition is more accurate and practical, and is widely used in clinical practice. We strictly selected our research objective according to this definition.

Table 4
Prediction of DRE-MRI (−).

	SE	SP	PLR	NLR	AUC
DRE-MRI (−)	83.87%	80.20%	4.24	0.20	0.886

DRE: drug-resistant epilepsy; MRI: magnetic resonance imaging; SE: sensitivity; SP: specificity; PLR: positive likelihood ratio; NLR: negative likelihood ratio; AUC: area under the curve.

Table 5
The DRE-MRI (−) scores and probability of DRE-MRI (−).

Scores	Probability of DRE-MRI (−) (%)
1	2.62
1.5	5.34
2	10.57
2.5	19.87
3	34.19
3.5	52.13
4	69.53
4.5	82.71
5	90.93
5.5	95.46

DRE: drug-resistant epilepsy; MRI: magnetic resonance imaging.

4.2. Predictors of DRE-MRI (−)

Electroencephalography is widely used for assessing the risk of recurrence after an unprovoked seizure, the likelihood of seizure relapse after AEDs are withdrawn, identification of epileptogenic regions in epilepsy surgery candidates, and for prediction of seizure relapse after surgery in MRI-negative and MRI-positive epilepsy [17]; EEG is closely related to the efficacy of the AEDs. Lamberink et al.'s study [34], which focused on seizure recurrence after withdrawal of AEDs, affirmed that the interictal spikes were factors affecting the efficacy. Zhang et al. [35] showed that the efficacy of levetiracetam on patients with newly diagnosed epilepsy could be predicted based on EEG features (sample entropy of α, β, θ, δ) using a support vector machine (SVM) model, which could guide AED selection. Two other studies found that EEG could predict a favorable response to AEDs [17,36], so our finding that EEG with epileptic discharge associated with DRE-MRI (−) in our study is reasonable. However, there are various findings on the use of EEG as a predictor of response to AEDs. Sample differences and the differences in design and methodology could all have contributed to the different results.

We also found that a history of CNS infections was an independent predictor of poor response to AEDs. Earlier studies also had similar observation [37]; CNS infection is an important cause of acute symptomatic seizures as well as subsequent epilepsy. Infections can promote acute symptomatic seizures and epileptogenesis by activating overlapping pathways with classical sterile inflammation (cytokines, chemokines, neurotransmitters, etc.), which by definition occurs in association with a brain damage or tissue injury. Usually, lesional postinfectious changes are associated with a higher risk of medically intractable epilepsy [38], depending also on localization and severity of the injury. Whereas, as described above for sterile inflammation, continuous stimulation of proinflammatory signals either by chronic inflammation or by seizures themselves may lead to a residual pathological state such as damaged blood–brain barrier, neuronal death, and persistent neuronal hyperexcitability—all of which may contribute to DRE [39]. Substructural postinfectious changes elevated mediators of chronic inflammation or cytokine levels play a vital role in DRE-MRI (−).

Factors such as IPIs (e.g., head trauma) are also associated with an AED response [6,10,12]. Five percent of all epilepsy and 20% of structural etiology in patients with epilepsy was posttraumatic epilepsy and was the leading cause of epilepsy in young adulthood (age 15–24 years) [40,41]. Christensen, et al. [42] found that the relative risk of developing epilepsy for people older than 15 years after mild and severe traumatic brain injury was 3.5 compared with no brain injury. Risk was still increased at 10 years after mild injury and after a mild brain injury were 1.5 and 2.2, respectively. Closed and/or mild head injury often produces diffuse concussive injury, with disconnection of axons and damage to vulnerable brain regions (such as the hippocampus) and blood–brain barrier disruption [43], for which medically intractable epilepsy would arise.

Our data suggested that >1 recurrence during the first 6 months after diagnosis remained a significant predictor of a higher risk of DRE-MRI (−), as previously reported [44]. The ILAE recommended that the efficacy of AED with newly diagnosed epilepsy were defined as a minimum of 6 months of seizure freedom [28,29]. Response to AEDs in the initial 6 months was a good predictor of long-term prognosis in patients with newly diagnosed epilepsy [45]. MacDonald and his colleagues [8] also found that the dominant clinical feature predicting remission was the number of seizures in the 6 months after diagnosis. Epidemiologist can make an accurate assessment of the chance of future long-term remission during the first 6 months after diagnosis.

4.3. DRE-MRI (−) scale

In the present study, we established a brief and convenient DRE-MRI (−) scale, only applicable to patients with MRI-negative epilepsy. We

did not include people with etiologic groups that are genetic and metabolic and epileptic syndrome because previous research suggests that those are almost all drug-resistant. This scale showed a good discrimination and met clinical requirements. Boonluksiri et al. established clinical prediction scoring of DRE in children with AUC of 0.76 [23]. Sungtae et al. [46] analyzed three machine learning models: Multivariate Logistic Regression, Linear Support Vector Machine, and Random Forest to predict DRE and the best model, random forest, only achieved an AUC of 0.764. Thus, our model was better than other reported CPRs. We also calculated the possibility of DRE-MRI (−) based on the score and the categorization of the risk score using 3 levels, which is a practical instrument that can be used at the bedside.

There are a number of potential limitations in our study. First, this was a single-center analysis with a small sample size. Second, we derived a scale in MRI-negative epilepsy, but we did not conduct internal and external validation. Thus, a multicenter, prospective study is required to expand the sample size and to validate the scale. Further, Multicenter collaboration is needed to use it in daily practice. Third, the features or variables extracted from patients were too small. The development of new learning techniques to extract more features is required to increase the capacity of risk stratification and predicting outcomes in patients with epilepsy. Fourthly, our study excluded the patients with etiologic groups that are genetic and metabolic and epileptic syndrome(see Lennox–Gastaut syndrome, Dravet syndrome, which are almost all drug-resistant), lacking of universality.

5. Conclusions

In conclusion, the DRE-MRI (−) scale may be a convenient and effective tool for predicting the response to AEDs in patients with newly diagnosed epilepsy. Applying this scale should help in selecting the best therapeutic schedule for patients with epilepsy.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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