Treatment response and its predictors among epilepsy patients: a retrospective cohort study

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Abstract

Background Epilepsy is a chronic neurologic disease with variable treatment responses. To design effective epilepsy treatment strategies, it is important to understand treatment responses and predictive factors. However, there are fewer data available in limited resource settings including Ethiopia. Objectives To assess treatment response and its predictors among adult epilepsy patients in Jimma university medical center, Ethiopia. Method and Materials A retrospective cohort study was conducted among 404 adult patients newly diagnosed with epilepsy and receiving antiepileptic medication between May 2010 to May 2015. Demographic, clinical, and outcome data of epilepsy patients with a follow-up of at least two years were collected. Data was entered into Epidata software and imported into the statistical package for the social sciences (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) for analysis. Cox regression was used to identify independent predictors of seizure remission. Result A total of 404 study participants were followed for 1579.25-person years (median 44.0 months). Of them, 64.6% remained seizure-free for at least one year. High frequency of pre-treatment seizure (adjusted hazard ratio [AHR]= 0.716, 95% CI: 0.558–0.919), poor early response (AHR= 0.339, 95% CI: 0.256–0.449), poor adherence (AHR= 0.719, 95% CI 0.546–0.942) and being on polytherapy (AHR= 0.563, 95% CI: 0.420–0.756) were significant predictors of poor seizure remission. Conclusion Only about two third of the patients achieved a one-year seizure remission period. High pre-treatment seizure frequency, poor early response, being on polytherapy and nonadherence to antiepileptic drugs were the independent predictors of poor seizure remission. Early identification and prediction of patients likely to be unresponsive based on the present findings need to be considered.

Background

Epilepsy is one of the common neurological brain disorders. It affects more than 69 million individuals globally, and about 80% of people with epilepsy are from low and middle-income countries [1, 2]. Epilepsy poses a substantial physical, social, and economic burden for the health systems and individuals [3, 4]. The risk of premature death from epilepsy increases two to three-fold compared to the general population [5].

Antiepileptic drugs (AEDs) are the mainstay of treatment, and about 70% of patients with newly diagnosed epilepsy achieve remission [6, 7]. The patient's response requires a careful diagnosis of seizure types, knowledge of pharmacotherapy and patient compliance to treatment [8]. Even though the treatment responses of epilepsy have been well studied in developed countries, limited data are available in developing countries including Ethiopia. The efficacy and tolerability of *AEDs* may vary among patients with different ethnicity [9, 10]. This makes extrapolating data of treatment response from developed countries difficult. In addition, the predictors of most newly diagnosed epilepsy treatment response is usually predictable early but predictors are highly variable across different populations [11]. Thus,

knowledge of epilepsy treatment responses and its predictors based on local data is vital to develop effective treatment strategies.

Currently, a large number of people with epilepsy live in Ethiopia. The prevalence of epilepsy in Ethiopia was reported to be 5.2- 29 .5 per 1,000 populations[12, 13], but data regarding epilepsy treatment response and its predictors are scanty in this population. The aim of the present study was to assess epilepsy treatment response and identify factors contributing to poor treatment response.

Methods

Study design and study setting

A retrospective cohort study was conducted among adult epilepsy patients on follow-up at the epilepsy clinic of Jimma university medical center (JUMC), which is the major public hospital in southwest Ethiopia serving for about 15 million people living in the catchment area.

Study population and data collection procedure

We included patients who met the definition of epilepsy based on the International League against Epilepsy (ILAE) report of 2014. The definition of epilepsy requires the occurrence of at least one seizure attack according to the ILAE[14].

All consecutive epilepsy patients who had regular follow up at the epilepsy clinic of JUMC from May 2010- May 2015 were recruited and followed until May 2017. The inclusion criteria were all newly diagnosed epilepsy patients, whose age was ≥ 18 years and patients who treated for at least two years. whereas the exclusion criteria were patients with follow up of < 2 years, patients who were transferred in from another facility like the health center or private clinic, patients who lost to follow up, and patients with incomplete medical records (i.e. patients with missing follow up data such as loss of initial chart).

Jimma university medical center started an electronic medical record of epilepsy patients in 2010. Since then a total of 639 adult epilepsy patients with newly diagnosed epilepsy were registered. A total of 404 patients have met the inclusion criteria among 639 patients who were diagnosed during the study period.

The data collection procedure was started by identifying the card number of the patients who started therapy within the specified period. An English version data abstraction format (checklist) was used to record relevant information like baseline patient characteristics, medication-related factors, and seizure control. The data abstraction tool was prepared after reviewing a different kind of literature [11, 15, 16].

Definition of terms and variables

Monotherapy: is defined as the use of one AED for treatment of epilepsy

Polytherapy: is defined as the use of more than one AED for the treatment of epilepsy

Seizure freedom/ remission: is defined as an attainment of at least one-year seizure-free period

Early remission: is defined as an achievement of seizure remission started immediately or in the first 6 months

Late remission: is defined as achievement of seizure remission, starting later than 6 months after treatment initiation.

Sustained remission: is defined as an achievement of seizure remission at any time after treatment and persisting until the end follow-up visit

Relapse: is defined recurrence of seizures after an initial remission

Terminal remission: is defined as at least a 1-year remission at the last follow-up visit, with or without previous relapses

Remitting-relapsing course: is defined as a seizure fluctuating between periods of seizure freedom and relapse

Worsening course: is defined as seizure continues after relapsing

No remission: is defined as no seizure remission through the entire follow-up period

Early response: is defined as the achievement of at least 6 months seizure freedom starting immediately from the time of initial therapy

Lost to follow up- is defined as missing three consecutive visits or not attending for ≥ six months

Treatment

The treatment given in the present study was done as part of standard care. The AEDs prescribed in the study include exclusively the old AEDs (phenytoin, phenobarbitone, carbamazepine, and valproate). Medication adjustment was done according to the patient response and tolerability. Adherence to medication was checked at each visit and recorded. More than 95% of medication adherence is necessary to prevent epileptic seizures and missing a single dose can provoke seizure [17]. Therefore, we classify patient adherence based on all or none rule. The patient is said to be adherent if there is no missed dose at all.

Follow-up and outcome

Patients were followed in 3-month intervals starting from the time of diagnosis untill the end of the study. At each follow-up visit, seizure frequency, medication, adverse effects, and adherence were routinely recorded. The follow-up data were extracted on a data record sheet developed for this study. We evaluated the response to drug therapy (seizure remission) at the end of follow-up by checking the occurrence of seizure after the initiation of treatment. According to ILAE seizure remission is defined as seizure freedom from all types of seizures for 12 months [6]. Hence, patients were categorized into two groups based on the achievement of one-year seizure freedom. Patients who had at least a one-year seizure remission were categorized into “remission group” and the remaining patients in the “no remission group”.

Data analysis

Data was coded and checked for completeness. The collected data was entered into a computer using the epi data management version 4.2.0. Data analysis was conducted using SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Data were presented using mean and median for quantitative variables or frequency and percentage for categorical variables. *Kaplan-Meier survival analysis was used* to compare treatment responses based on the different variables. Multivariable Cox regression was run using forward wald method to identify the best independent predictors of remission. A p value of <0.05 was used to declare a statistically significant association.

Results

Demographic and clinical characteristics of patients

We identified 639 patients with newly diagnosed epilepsy between May 2010 and May 2015 from the hospital record. Among these, 404 patients have fulfilled our inclusion criteria and included in the final analysis (Fig. 1). Of the included patients, 60.1% were male. The mean age at onset was 27.40 ±11.147 years. Generalized *epilepsy* was the most predominant type of epilepsy accounting for 78.7% of the cases. More than half (63.86%) of the patients had more than five episodes of seizures at the time of diagnosis. The cause of epilepsy was idiopathic/cryptogenic in the majority (86.1%) of the patients and fewer patients had symptomatic epilepsy caused by head trauma, stroke, central nervous system infection, and brain tumor. A family history of epilepsy was present in 9.7 % of cases.

Phenobarbital was the commonest prescribed drug (39.4%) as an initial drug, followed by phenytoin and carbamazepine. Of the total patients, 56.2% were on monotherapy and the rest were on polytherapy taking two or three drugs. Comorbid illness (depression, human immunodeficiency virus, dyspepsia, anxiety, bipolar disorder, psychosis, asthma) were reported by 13.4% of patients. Status epilepticus

occurred in 4.7% of the patients. Early response to AEDs occurred in more than one-third of the patients. More than sixty percent of the patients were adherent (table 1).

Follow up assessment

Patients were followed for 1579.25-person-years. The median duration of the follow-up was 44.0 months (3.6 years) (range 2 – 7 years). All patients were followed for at least 2 years, 203 (50.3%) patients for at least 4 years and 99 (24.5%) for at least 6 years.

Prognosis of patients with newly diagnosed epilepsy

Overall, 261(64.6%) of the patients achieved seizure freedom for at least one year. The remaining 143 (35.4%) patients never experienced remission while continuing treatment. As shown in Fig.2 an analysis was made to look for the prognostic patterns of the patients. Early and sustained remission, late but sustained remission, remitting-relapsing course and no remission were observed in 17.58%, 9.4%, 37.63 and 35.39% of patients respectively.

Analysis of predictors related to poor seizure remission

Cox regression was conducted to identify the independent predictors of poor seizure remission. In the univariate Cox regression analysis, number of seizures prior to AED treatment (crude hazard ratios (CHR)= 0.566, 95C%CI: 0.443–0.722), adherence to AEDs (CHR= 0.527, 95%CI: 0.405–0.686), early response to AED therapy (CHR= 0.239 95C%CI: 0.185–0.308], the presence of adverse event (CHR= 0.669, 95C%CI: 0.519–0.864) and the type of treatment (CHR= 0.363, 95C%CI: 0.277– 0.475) were significant predictors. However, in subsequent multivariable Cox regression analysis, four variables remained independently associated with poor seizure remission. High frequency of pre-treatment seizure (adjusted hazard ratios (AHR) = 0.716, 95% CI: 0.558–0.919), poor early response to AED therapy (AHR = 0.339, 95% CI: 0.256–0.449), poor adherence to AED therapy (AHR= 0.719, 95% CI: 0.546–0.942) and patients who were on polytherapy (AHR= 0.563, 95% CI: 0.420–0.756) were at high risk of poor seizure remission. (table 2).

The Kaplan-Meier analysis for the cumulative probability of not achieving seizure remission for all variables was conducted. Those variables with the significant association are presented below (fig. 3–6).

Discussion

The present study was designed to determine the response of epilepsy patients with the care provided in a resource-limited setting. We observed that only 261(64.6%) patients achieved seizure-freedom for at least one year. Prior studies showed that a higher seizure remission rate compared to the present study. In a study conducted by Zhang et al in China, 80% seizure remission was observed[18]. Similarly, a slightly higher remission rate (69.1%) was reported by Shen et al [7]. On the other hand, seizure remission was reported as low as in 43.6% of patients in a study by Rizaldy et al [19]. A possible explanation for the

inconsistency of these studies could be mainly due to methodological differences, such as the duration of remission criteria used, difference in the period of follow-up and difference in settings.

In the current study based on patterns of response, 46 % of the patients entered early remission, around one-fifth entered late remission, two out of three had remission followed by relapse and more than one-third never entered remission. In a study by Shen et al early remission was achieved in 51.6%, and late remission was subsequently achieved in 17.5% of patients [7]. Another study in Italy reported that 56.2% entered 2-year early remission [20]. These results are slightly higher compared to the current study. Similarly, 35.39% of patients in our study had never achieved remission. In contrast to our findings, previous studies reported a lower proportion of patients with no remission ranging from 15–30.9%. [7, 11, 15, 18]. In general, despite the differences in the definition of the patterns, the current study found lower total remission (early and late) and a higher percentage of patients with no remission. There are several possible explanations for these findings. The use of only old AEDs, genetic variations, the difference in patient characteristics, lack of qualified neurologists, and poor health system infrastructure in our setting could possibly contribute to this discrepancy. Moreover, exclusion of nonadherent patients in some of the studies could result in a higher remission rate.

Another aim of the project was to identify the predictor of seizure remission in epilepsy patients. The number of seizures prior to AED treatment, early response to AED therapy, adherence to AEDs, and the treatment type (polytherapy vs monotherapy) were the predictors of remission. We demonstrated that patients with a high frequency of pre-treatment seizure were associated with poor treatment seizure remission (AHR 0.716, 95% CI 0.558, 0.919). In accordance with the present results, previous studies have demonstrated that a higher pre-treatment seizure frequency has been repeatedly associated with a lower chance of remission [19-24]. The role of the number of pre-treatment seizure was based on the theory that prolonged and recurrent seizure caused neuronal damage and the development of new epileptic foci [25]. A significant difference was observed in a study by Del Felice et al [20], in which the remission was lower in patients with a higher frequency of seizure. This indicates seizure must be recognized soon, and optimal treatment is needed for preventing injury, premature death, cognitive impairment, and psychosocial stigma [23, 24].

Early response to the initial AED therapy was significantly associated with seizure remission. In agreement with our study, a poor early response to the first drug has been established by others as a predictor [11, 15, 26]. Similarly, poor patient adherence to AEDs was a significant predictor of poor remission. This finding is consistent with those of other prospective and retrospective cohort studies and suggests that poor adherence is a major cause of uncontrolled seizure[19, 27].

Another important finding was that the association between the number of AEDs used and seizure remission. Comparing to patients on monotherapy patients who were on polytherapy had a poor remission. In line with our study, a study conducted by Melaku [28], reported that the likelihood of developing controlled seizure was decreased by 63.2 % (AOR = 0.368, CI: 0.210, 0.646) in patients with polytherapy compared to monotherapy. Another study by Ashmawi et al [15], also reported as the higher the number of drugs used, there was a lower probability of remission. It is important to bear in mind the possible bias in these responses. Patients who are not responding to the initial drugs are likely to receive polytherapy and may overestimate the non-remission rate. However, it has proved in randomized clinical trials that there was no advantage of polytherapy over monotherapy in the reduction of seizure frequencies [29]. The combination of older AEDs does not necessarily lead to a better reduction of seizures and may increase the tendency to side effects [30]. However, in refractory epilepsy, polytherapy may be advantageous.

The findings of our study have some important implications for clinical practice. Firstly,

our study found that high pre-treatment seizure frequency was a predictor of poor seizure remission. This is because patients did not visit health facilities until they experience several seizures. Therefore, activities such as awareness campaigns and dissemination of information through media are needed to decrease the delay in epilepsy treatment. Secondly, non-adherent patients were at high risk of poor remission. Thus, all healthcare providers should deliver health education to prevent AEDs nonadherence. Thirdly, the association of poor early response (response within the first 6 months) in our study implies attention should be given during the first six months of treatment.

Finally, some important limitations need to be considered. The retrospective nature of the study, data extracted from the secondary source was subject to missing important characters such as family history and incompleteness. However, attempts were made to exhaustively find the variables everywhere in the record from initial follow up to the end. The other limitation of this study was the inclusion of nonadherent patients that might reduce the remission rate. However, exclusion of these patients may result in the unpowered sample as a high number of patients were nonadherent. Moreover, including these patients will help to mimic the real-world experiences of our patients. Despite these limitations, our study provides an interesting look at the overall seizure remission from the treatment of epilepsy in a resource-limited setting.

Conclusions

Our study showed that about two third of the patients had achieved a one-year seizure remission. High pre-treatment seizure frequency, being on polytherapy, poor early response and nonadherence to treatment were the independent predictors of poor seizure remission. Patients with these characteristics should receive optimal pharmacologic treatment and frequently follow up.

Abbreviations

AEDs- Antiepileptic drugs

AHR- Adjusted hazard ratio

CHR- Crude hazard ratios

JUMC- Jimma university medical center

ILAE- International League against Epilepsy (ILAE)

Declarations

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Availability of data and materials

The dataset of this article is accessible on a reasonable request from the corresponding author.

Ethical approval and consent to participate

This study was approved by the institutional review board (IRB) of Jimma university, college of health sciences. A written consent was obtained to access patient medical records from the medical director of the hospital. The privacy of personal information was strictly conserved.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All the mentioned authors were involved in this research project. KG created and designed the study, performed analysis and interpretation of data with manuscript preparation, FB and LC assisted in study

design, data analysis, and manuscript evaluation, TD assisted in data analysis and manuscript evaluation. All authors read and accepted the final manuscript.

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Authors' contributions

All the mentioned authors were involved in this research project. KG created and designed the study, performed analysis and interpretation of data with manuscript preparation, FB and LC assisted in study design, data analysis, and manuscript evaluation, TD assisted in data analysis and manuscript evaluation. All authors read and accepted the final manuscript.

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Tables

Table 1: Demographic and clinical characteristics of patients

Characteristics	Category	Remission (%)	No remission (%)	Total Frequency (%)
Sex	Male	161(39.9)	82(20.3)	243(60.1)
	Female	100(24.8)	61(15.1)	161 (39.9)
Family history of epilepsy	Yes	23(5.7)	17(4.2)	39 (9.7)
	No	158(39.1)	75(18.6)	233 (57.7)
	NA	80(19.8)	51(12.6)	132 (32.7)
Age at onset of seizure	<30	168(41.6)	97(24)	265 (65.6)
	30–44	59(14.6)	34(8.4)	93 (23)
	≥ 45	34(8.4)	12(3)	46 (11.4)
Pretreatment number of seizures	<= 5 seizures	115(28.5)	31(7.7)	146(36.1)
	> 5 seizures	146(36.1)	112(27.7)	258(63.9)
Pre-treatment duration	≤ 12 months	165(40.8)	77(19.1)	242 (59.9)
	>12 months	96(23.8)	66(16.3)	162 (40.1)
Seizure type	Generalized	205(50.7)	113(28)	318 (78.7)
	Focal seizure	14(3.5)	6(1.5)	20 (5.0)
	Undetermined	42(10.4)	24(5.9)	66 (16.3)
Etiology	Symptomatic	36(8.9)	20(5)	56 (13.9)
	Idiopathic/cryptogenic	225(55.7)	123(30.4)	348 (86.1)
Neurologic examination	Normal	234(57.9)	118(29.2)	352 (87.1)
	Abnormal	27(6.7)	25(6.2)	52 (12.9)
Treatment type	Monotherapy	183(45.3)	44(10.9)	227 (56.2)
	Polytherapy	78(19.3)	99(24.5)	177 (43.8)
Early response to AED therapy	Yes	131(32.4)	11(2.7)	142 (35.1)
	No	130(32.2)	132(32.7)	262 (64.9)
Adherence to AEDs	Good	179(44.3)	67(16.6)	246 (60.9)
	Poor	82(20.3)	76(18.8)	158 (39.1)
Adverse events	Yes	93(23)	70(17.3)	163 (40.3)
	No	168(41.6)	73(18.1)	241 (59.7)
Comorbidities	Yes	38(9.4)	16(4)	54 (13.4)
	No	223(55.2)	127(31.4)	350 (86.6)
Status epilepticus	Yes	12(3)	7(1.7)	19 (4.7)
	No	249(61.6)	136(33.7)	385 (95.3)

AED: Antiepileptic drugs

Table 2: Predictive factors of poor seizures remission among people with epilepsy

Characteristics	Category	CHR (95% CI)	AHR (95% CI)
Sex	Female	1	
	Male	1.108 [0.863, 1.422]	
Family history of epilepsy	No	1	
	Yes	0.708 [0.457, 1.097]	
	NA	0.793 [0.606, 1.038]	
Age category at onset of seizure	<30	1	
	30-45	1.026 [0.762, 1.380]	
	≥ 45	1.308 [0.904, 1.892]	
Pretreatment number of seizures	≤ 5	1	
	>5	0.566 [0.443, 0.722]	0.716 [0.558, 0.919]
Pre-treatment duration	≤ 12 months	1	
	>12 months	0.880 [0.684, 1.131]	
Seizure type	Generalized	1	
	Focal seizure	1.272 [0.739, 2.188]	
	Undetermined	1.026 [0.736, 1.431]	
Etiology	Symptomatic	1	
	Idiopathic/ Cryptogenic	0.866 [0.614, 1.223]	
Neurologic examination	Normal	1	
	Abnormal	0.708[0.475, 1.055]	
Treatment type	Monotherapy	1	
	Polytherapy	0.363 [0.277, 0.475]	0.563 [0.420, 0.756]
Early response to AED therapy	Yes	1	
	No	0.239 [0.185, 0.308]	0.339 [0.256, 0.449]
Adherence	Good	1	
	Poor	0.527 [0.405, 0.686]	0.719 [0.546, 0.942]
Adverse events	Yes	0.669 [0.519, 0.864]	
	No	1	
Comorbidities	Yes	1.244[0.881, 1.756]	
	No	1	
Status epilepticus	Yes	1.036 [0.581, 1.850]	
	No	1	

AED: Antiepileptic drugs, CHR: Crude hazard ratio, AHR: Adjusted hazard ratio 1: Stands for reference

Figures

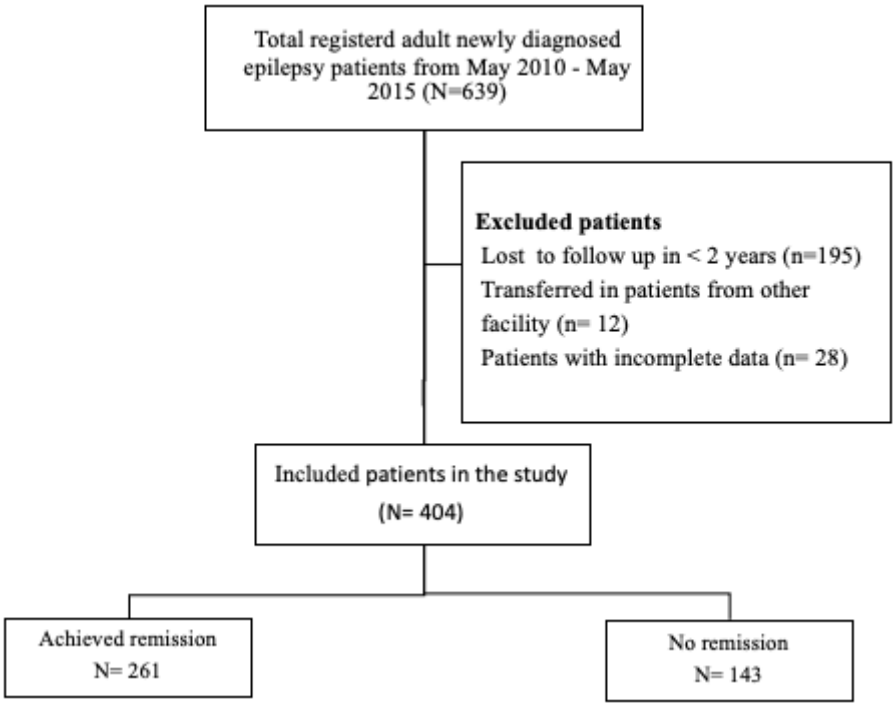

Figure 1

Flow diagram of patients included in the study

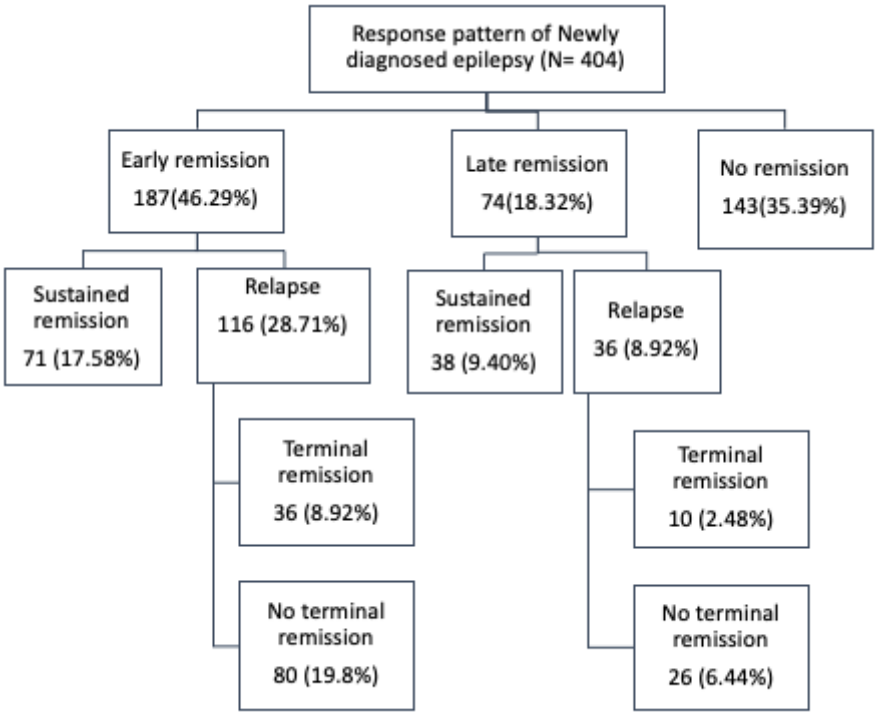

Figure 2

Prognosis of patients with newly diagnosed epilepsy

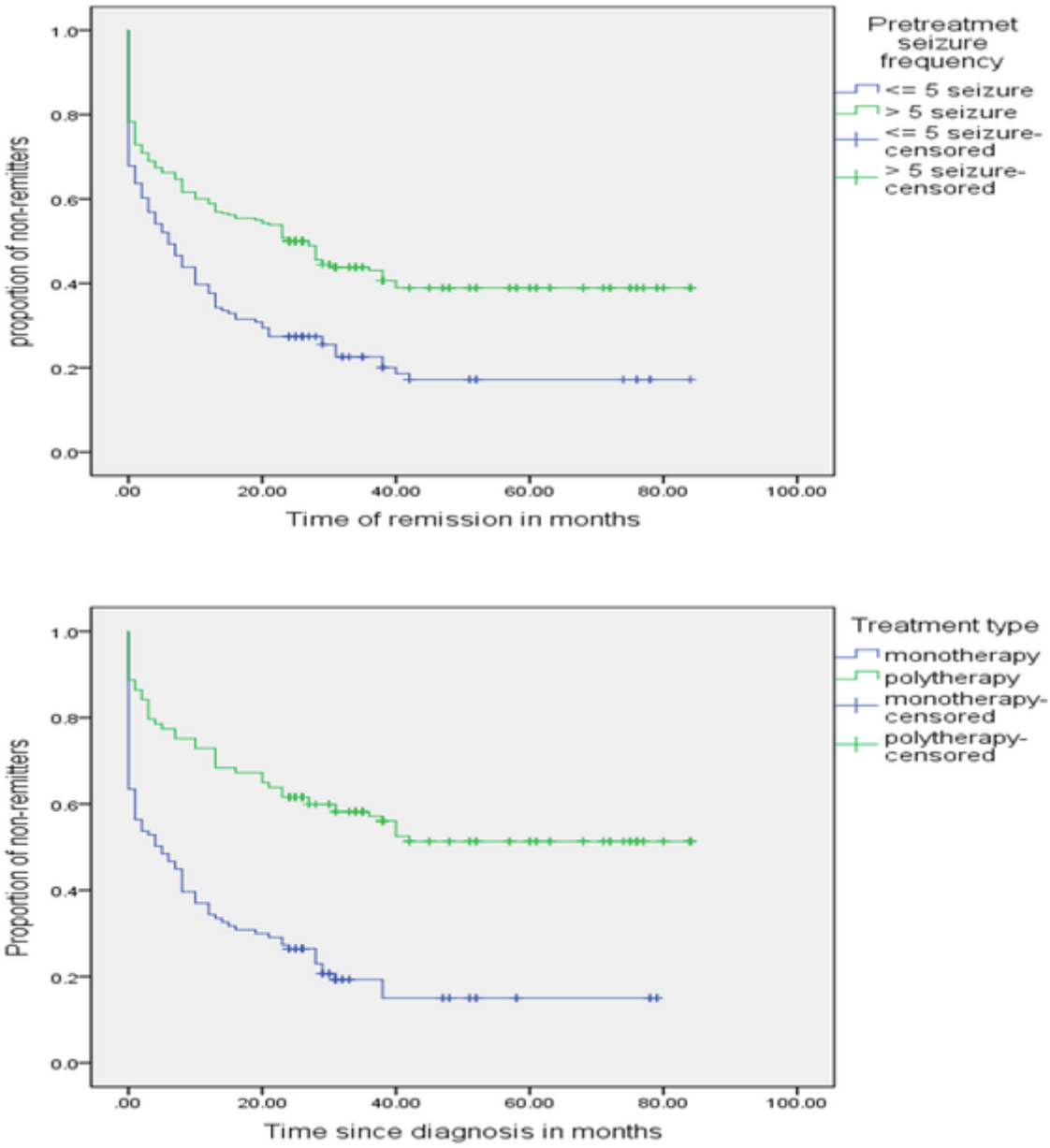

Figure 3

Kaplan-Meier analysis for the cumulative probability of not reaching seizure remission based on pre-treatment seizure (P log rank < 0.001)