Determination of The Factors Leading to Non Adherance With Anti-Epileptic Medication In Psychatric Ambulatory Follow Up Patients Of Mettu Karl Referral Hospital, South Western,Ethiopia: A Prospective Cross Sectional Study

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ABSTRACT: *Epilepsy is a chronic disorder or group of chronic disorder in which the indispensable feature is recurrence of seizures that are typically unprovoked and usually unpredictable. Nonadherence of epileptic patients to anti-epileptic medication often leads to an increased risk of seizures and worsening of disease, death and increased health care costs. To ascertain determination of the factors leading to nonadherence with anti-epileptic medication in psychiatric ambulatory follow up patients Mettu Karl Referral Hospital. A prospective cross sectional study design was carried out from March 02 /2021 to May 03/2021.Data was collected through employing check list and semi-structured questioner, and then the collected data was cleared, coded and analyzed by statistical packages for social sciences 25.0 version statistical software. A p-value of less than 0.05 is considered statistically significan. The prevalence of poor adherence to AED therapy was documented in 63.1%. The majority of patients with poor adherence to AEDs were unable to read and write 51(45. 9%).According to MMAPS-8 score,65(58.6%),21(18.9%), and 25(22.5%) of the participants had a score of low adherence, medium adherence and high adherence respectively. Factors like duration of treatment above 5 years, patient age between 25-44 years old, divorced marital status, those who had follow up every two months, patients who acquired medication out of pocket, who had co-morbidity, and side effects of AEDs were the independent predictors of AEDs non-adherence. In our study, side effect of anti-epileptic drugs was the most common reason for non non-adherence and regimen complexity was the least common reason. Health care should have to maximize communication strategies with the patients about their medication are necessary to improve adherence and to avoid the clinical consequences of poor adherence.*

KEYWORDS: Epilepsy, Nonadherence, Adult, Mettu Karl Referral Hospital, Ethiopia.

INTRODUCTION

Epilepsy is a chronic neurologic disorder characterized by repeated epileptic seizures attacks which result from paroxysmal uncontrolled discharges of neurons within the central nervous system[1].The definition of epilepsy requires the occurrence of at least one epileptic

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seizure[2].Epilepsy is a chronic disorder of the brain and is one of the most common serious neurological disorders affecting 50 million people worldwide with no boundary to age, race, social class, nationality, or geographical location [3].Among patients who had epilepsy,85% of them found in developing countries and estimated 40 million people do not receive appropriate treatment[4].Many Africans believe epilepsy is contagious. As a result of this, they are unwilling to help or touch the person who has fall enduring seizure. This Kind of belief worsens the stigma [5].The magnitude of anti-epileptic drug nonadherence is ranged from 26% in USA to 67% in Nigeria [6].Despite a high prevalence of epilepsy in LMICs, most people do not receive appropriate treatment. This is due to limited knowledge, poverty, cultural beliefs, stigma, poor health delivery infrastructure, and shortage of trained health care workers[7].The ultimate goal of treatment for epilepsy is no seizure episode and no side effects with having and optimal quality of life. Therefore, the management should be individualized to eliminate seizures or reduce seizure frequency, while avoiding drug interactions and side effects as well as prevent other complications and achieve the best possible quality of life[8].AEDs can be indicated for patients who have had one or more epileptic seizures. The choice of therapy for the management of epilepsy varies depending on the type, frequency, and severity of the seizures. Making an accurate diagnosis of the type of epilepsy is crucial to select the best therapy [9]. Medication nonadherence is a voluntary or involuntary behavior of medication intake which includes failing initially filling or refilling a prescription, discontinuing a medication before the course of therapy is completed, inability to adhere with agreed recommendations from health care provider, taking more or less of a medication than prescribed, and taking a dose at wrong time [10].Studies regarding adherence have found four primary factors associated with medication non-adherence: patient related factors(e.g, socio-economic characteristics, and perceptions and beliefs),illness-related factors (e.g., severity of illness and frequency of symptoms),medication-related factor s (e.g., number of daily doses, efficacy, and side effects),and physician-related factors (e.g, patient-physician relationship)[11].Non-adherence to anti-epileptic medications has been reported to be high. Studies showed a High prevalence of seizure(21–45%) inpatients who did not adhere to their anti-epileptic medications [12]. Failure to adhere through forgetfulness, misunderstanding, or uncertainty about clinician's recommendations, or intentionally due to their own expectations of treatment, side-effects, and lifestyle choice are found to be the reasons for non-adherence[13].

Globally, about 69 million people have epilepsy and subsequently become one of the largest neurological diseases; about 90% of epileptic patients in developing countries are not receiving appropriate treatment due to the cultural attitude, lack of prioritization, poor health care system, economic problem and inadequate supply of AEDs[14].Studies in India reported that 36% of prescriptions were irrational as per the global standard ILAE guidelines[15].A study from Ethiopia found about 58% of the patients who developed GTCS at baseline evaluation with the frequency of $\leq$ 8 times,23.2% of them died [16].Due to the unfavorable attitude towards a person with epilepsy, many people do not want to work and live a person living with epilepsy. Large numbers of people do not want even to shake hands with epileptic individuals. Individuals with an unfavorable attitude try to keep their children away from these patients. A person living with epilepsy may also have perceived stigma [17]. Unfavorable attitude and poor knowledge continue to root a negative influence on the management of epilepsy in African countries. The disorder

leads to irrational belief, discrimination, and stigma in many of African countries. Spiritual and sociocultural dogmas influence the type of treatment received by individuals with epilepsy and epilepsy in the most reported reason for school rejection as it seen contagious and shameful[18].Poor adherence to AED therapy is associated with higher risk of mortality compared to patients who adhere to their medication. Several factors have been found to be associated with treatment outcome in epilepsy. These include; gender, age of seizure onset, type of epilepsy, seizure frequency, etiology of epilepsy, duration of epilepsy, electroencephalography abnormality and presence of comorbidities [19].Therefore this study will intended to ascertain determination of the factors leading to nonadherence with anti-epileptic drug in psychiatric ambulatory follow up patients

METHODOLOGY

Study design, area and Period
This was an institution based prospective cross-sectional study carried out at the psychiatry ambulatory clinic of Mettu Karl Referral Hospital. All the patients with epilepsy attending ambulatory outpatient Clinic between a period of three months extending from March 02 /2021 to May 03/2021 were analyzed. The hospitals located in Mettu town, South western Zone, Oromia Regional state, located at 600 km from Addis Ababa.

Inclusion and exclusion criteria
Patients who had follow-up at adult psychiatric clinics of MKRH and diagnosed as seizure disorder or Epilepsy, patients who had been on AEDs treatment for at least 2 months, patients who had complete medical records, patients who were willing to participate in the study were included in the study and patients without confirmed diagnosis, patients who had interrupt their follow up during data collection. Patients who had emergency condition such as current aggravated and unconscious condition and capable of impairing response were excluded.

Sample size determination and sampling procedure
The sample size was determined by using the Single Population proportion Formula: The sample size was determined based on"P"value which was taken from Northwest Ethiopia, P=0.378, or 37.8%., n=sample size, P=prevalence of non-adherence to AEDs, d=margin of sampling error tolerated, z=the standard normal value at confidence interval of 95%. n = $(1.96)^2(1- 0.378)$ x $(0.378)/(0.05)^2$=361.Since the total number of epileptic patients was less than 10,000, reduction formula (correction formula) was applied as follow; $n_f=n/(1+(n/N))$,$n_f=361/(1+(361/141))$ =101.When 10% contingency is added to minimize non response rate, then final sample size was found to be 111.Purposive sampling technique was used to recruit samples for the study in each day of the data collection process until the desired sample size was obtained.

Study variables
Based on our study the dependent variable is nonadherence of patients to their AEDs and independent variable is demographic variables (age, sex, educational status, marital status,

occupation, place of residence, source of medication),patient characteristics (type and number of prescribed AEDs, duration of treatment with AEDs, seizure free period and co morbid conditions).

Data collection procedure
Data was collected by interviewing participants and reviewing patient charts using structured questionnaire by trained data collectors. The checklist had two parts. Part I (case identification),and part II (subjective data, objective data, laboratory results, assessment, prescribed medications and Adherence of epileptic patients was measured using a Morisky Medication Adherence Scale-8 (MMAS-8)).The MMAS-8 is a generic self-reported, medication-taking behavior scale, used for a wide variety of medical conditions. It consists of eight items focusing on past medication use patterns with a scoring scheme of "Yes"=1and "No"=0.Conversely,for item 5,a score of zero was given for a negative response whereas a score of one was given for a positive response (Yes=1;No=0).For questions 1,2,3,4,6 and 7,a score of zero was given for a positive response whereas a score of one was given for a negative response(Yes=0 and No=1).The last item has a five-point Likert response that was used with options "never", "once in a while", "sometimes", "usually", and "always." In this Likert scale, values' ranging from 0 to 1 was given at a specified interval of 0.25 with "0" given for "never" and "1" given for "always". The items were then summed up to give a range of scores from high adherence to low adherence with a maximum score of 8. The items scores were scaled as: 3-8 low adherences; 1-2 medium adherences and 0 as high adherence. In our study, patients with a score of low adherence were considered as non-adherent; medium adherence and high adherence were considered as adherent.

Data analysis
The gathered quantitative data was cleared, arranged, coded, and then analyzed through employing statistical packages for social sciences version 25.0 statistical Software. Categorical variables were expressed by percentage and frequency, whereas continuous variables were present by mean and standard deviation. Bivariate and multivariable logistic regression was used to analyze the associations between dependent variable and independent variables. Independent variables with p < 0.25 in uni-variable binary logistic regression analysis were re-entered into a multivariable binary logistic regression model to identify associated factors of treatment non-adherence in epilepsy. A p-value of less than 0.05 is considered statistically significant in all analyses.

Ethical considerations
A formal letter was obtained from SWAN diagnostic pharmaceutical importer, and given to MKRH in order to get permission to conduct the study, and all the process was started after getting permission from MKRH.A letter was submitted to MKRH management then transferred to concerned bodies like Doctors and Psychiatry who was working in the ambulatory clinic of the hospital. Privacy and behind the scenes was ensured during data collection process. The instruments and procedure will not cause any harm to the study subject. Thus, name and address of the patient was not recorded in data collection checklist.

Operational definition
Adherent: If the MMAS - 8 score was ≤ 2.
Non-adherent: If the MMAS - 8 score was > 2.
Controlled seizure: Seizure free period of ≥ 2 years.
Uncontrolled seizure: Seizure free period of < 2 years.

Unclassified seizure: The diagnosis was documented as epilepsy/seizure disorder without any classification.

ADRs: Any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy and bothersome adverse effects complained by the patient, was included.

RESULTS

Social-demographic and socioeconomic status information
The prevalence of poor adherence to AED therapy was documented as 63.1% of the study subjects (n =111). From 111 study subjects, 69(62.2%) were men,55(49.5%) of patients aged 19-25 years old and 67(60.4%) of patients were earn monthly income less than/equal to 1500 Ethiopian birr. Above half 60(54.1) of respondents were dwell in urban, and only few 9(8.1%) of respondents were pregnant. The majority of patients with poor adherence to AEDs were unable to read and write 51(45.9%), unemployed 72(64.9%), Single 47(42.3%), and 37(33.3%) had the history of social substance use (table 1).

Table 1: Social-demographic and socioeconomic status information of epileptic patients, in MKRH, Southwestern, Ethiopia (n= 111)

Variables	Category	Frequency	Percent
Age	19-25 years	35	31.5
	26-44 years	55	49.5
	≥45 years	21	18.9
Sex	Male	69	62.2
	Female	42	37.8
Residency	Urban	60	54.1
	Rural	51	45.9
Monthly income	< 1500	67	60.4
	≥1500	44	39.6
Pregnancy	Yes	9	8.1
	NO	102	91.9
Educational status	Unable to read and write	51	45.9
	Grade 1-8	25	22.5
	Grade 9-12	25	22.5
	College and above	10	9.0
Occupational status	Employed	13	11.7
	Unemployed	72	64.9

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	Others	26	23.4
Marital status	Single	47	42.3
	Married	33	29.7
	Divorced	26	23.4
	Widowed	5	4.5
Prevalence of non-adherence to AEDs	Yes	70	63.1
	No	41	36.9
Social substance use	Ye	37	33.3
	No	74	66.7

Clinical characteristics of epileptic patients

According to MMAPS-8 score, 65(58.6%), 21(18.9%), and 25(22.5%) of the participants had a score of low adherence, medium adherence and high adherence respectively. From the participants, less than half of respondents were have laboratory values 44(39. 6%), drug-interaction 16(14.4%), past medical history 289(25.2%), past medication history 27(24.3%), comorbidity 34(30.6%) (Table2).

Table 2: Clinical characteristics of epileptic patients in MKRH, Southwestern, Ethiopia (n=111)

Variables	Category	Frequency	Percent
MMAPS-8	Low	65	58.6
	Moderate	21	18.9
	High	25	22.5
Laboratory values	Yes	44	39.6
	No	67	60.4
Drug-interaction	Yes	16	14.4
	No	95	85.6
Past medical history	Yes	28	25.2
	No	83	74.8
Past medication history	Yes	27	24.3
	No	84	75.7
Comorbidity	Yes	34	30.6
	No	77	69.4

Distribution of patients with epilepsy disorder by treatment related factors
Majority of the respondents, 35 (31.5%), had unclassified seizure and 35 (31.5%) was taken Phenobarbital for epilepsy. Slightly less than half 50(45.0%)of the participants were have khat addiction from social substance use, and 92(82.9%)getting medication out of pocket. Half 55(49.5%) of the participants were on monotherapy and 61(55.0%) were pursue their follow up in 2 months. About slight half,50(45.0%),of the participants have been taking anti-epileptic medication(s) for > 1 year up to 5 years, and their duration of epilepsy during last year were 1-5 times 43(38.7%).More than one-half 65(58.6%) of participants had duration of age of onset less than/equal to 10 years (Table 3).

Table 3: Distribution of patients with epilepsy disorder by treatment related factors in MKRH, Southwestern, Ethiopia (n=111)

Variables	Category	Frequency	Percent
Social substance use	Alcohol	20	18.0
	Khat	50	45.0
	Smoking	26	23.4
	Others	15	13.5
Duration of epilepsy during last year	Zero	19	17.1
	1-5 times	43	38.7
	6-10 times	31	27.9
	Greater than 10 times	18	16.2
Type of epilepsy	Focal seizure	20	18.0
	Generalized tonic-clonic	16	14.4
	Absence seizure	15	13.5
	Myoclonic seizure	25	22.5
	Unclassified seizure	35	31.5
Number of anti-epileptic drugs	One	55	49.5
	Two	56	50.5
Type of anti-epileptic drugs	Phenytoin	16	14.4
	Phenobarbital	35	31.5
	Carbamazepine	25	22.5
	Phenobarbital +Carbamazepine	15	13.5
	Phenytoin + Carbamazepine	15	13.5
	Others	5	4.5
Duration on treatment	2 months-1 year	26	23.4
	> 1 year up to 5 years	50	45.0
	> 5 years	35	31.5p
Getting medication	Free	19	17.1
	Payment	92	82.9
Duration of age of onset	≤ 10 years	65	58.6
	11 years-30 years	21	18.9
	> 30 years	25	22.5
Frequency of follow up	2 months	61	55.0
	Once a month	30	27.0
	Every two months	20	18.0
Side effects	Yes	68	61.3
	No	42	37.8

Reasons for AEDs medication non-adherence

Fear of AEDs adverse events 18.9% were the most reasons for medication non adherence followed by drug product non-availability 14.4%, and drug complexity 3.6% were the least reasons for medication non-adherence (table 4).

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Table 4: Reasons for AEDs medication non-adherence in MKRH, South western, Ethiopia (n=111)

Variables	Frequency	Percent
Fear of adverse events	21	18.9
Disbelief in drug effectiveness	10	9.0
Directions not understood	7	6.3
Patient forgets to take	9	8.1
Patient felt better	5	4.5
Patient felt worse	10	9.0
Drug product too expensive	15	13.5
Patient cannot swallow	11	9.9
Drug product not available	16	14.4
Regimen complexity	4	3.6
Others	3	2.7

Factors associated with anti-epileptic drug nonadherence among people with epilepsy
Prevalence of non-adherence was highest among patient 25-44 years old were (AOR: 1.84; 95%CI: 0.079-2.896; P=0.009) 2 times more likely non-adherent to AEDs. Regarding marital status divorced(AOR:3.215;95%CI:1.413-2.493;P=0.001) were 3 times more likely have poor adherence than others category of marital status, and students who learnt grade 1-8(AOR:1.839; 95%CI:0.094-1.74; P=0.001) were 2 times more likely had non-adherence, and also those who had follow up every two months (AOR:3.267;95%CI:1.091-4.869;P=0.024) were 3 times more likely had poor adherence. Patients who acquired medication out of pocket (payment) (AOR: 4.021; 95%CI: 3.154-9.045; P=0.005) were 4 times more likely affect the AEDs adherence, and who had co-morbidity (AOR: 1.650; 95%CI: 0.914-2.153; P=0.001) were 1.5 times more likely decrease AEDs than those who hadn't co-morbidity. Regarding duration of treatment respondents who were take AEDs for above 5 years (AOR: 2.015; 95%CI: 0.698-2.436; P=0.004) were 2 times more likely non-adherent. Side effects (AOR: 3.01; 95%CI: 1.927-7.026; P=0.001) were 3 times more likely affect AEDs adherence (table 5).

Table 5: Factors associated with anti-epileptic drug nonadherence among people with epilepsy, in MKRH, Southwestern, Ethiopia (n=111)

Variables	Category	N (%)	AOR (95% C.I)	P-value
Age	19-25 years	35(31.5)	ref	
	25-44 years	55(49.5)	1.84(0.079-2.896)	0.009**
	≥45 years	21(18.9)	0.089(0.178-1.786)	0.896
Sex	Male	69(62.2)	ref	

	Female	42(37.8)	0.53(0.076-1.068)	0.145
Income	<1500 ETB	67(60.4)	ref	
	≥1500 ETB	44(39.6)	0.298(0.896-1.187)	0.073
Marital status	Single	47(42.3)	ref	
	Married	26(23.4)	1.14(1.014-1.742)	0.461
	Divorced	33(29.7)	3.215(1.413-2.493)	0.001**
	Widowed	5(4.5)	0.42(0.456-2.672)	0.013*
Educational status	Illiterate	51(45.9)	ref	
	Grade 1-8	25(22.5)	1.839(0.094-1.74)	0.001**
	Grade 9-12	25(22.5)	0.234(1.436-2.543)	0.059
	Diploma and above	10(9.0)	1.04(1.570-1.629)	0.541
Social substance use	Yes	37(33.3)	ref	
	No	74(66.7)	1.57(0.736-1.821)	0.758
Frequency of follow up	2 months	61(55.0)	ref	
	Once a month	30(27.0)	0.079(1.849-1.034)	0.314
	Every two months	20(18.0)	3.267(1.091-4.869)	0.024*
Duration of treatment	2 months-1 year	26(23.4)	ref	
	1 year up to 5 years	50(45.0)	1.104(0.276-1.948)	0.714
	Above 5 years	35(31.5)	2.015(0.698-2.436)	0.004**
Getting medication	Free	19(17.1)	ref	
	Payment	92(82.9)	4.021(3.154-9.045)	0.005**
Comorbidity	Yes	34(30.6)	ref	
	No	77(69.4)	1.650(0.914-2.153)	0.001**

Number of anti-epileptic drugs	One	55(49.5)	ref	
	Two	56(50.5)	1.049(0.047-1.906)	0.276
Side effects	Yes	68(61.3)	ref	
	NO	42(37.8)	3.01(1.927-7.026)	0.001**

AOR: Adjusted odd ratio; CL: Confidence interval; COR: Crude odd ratio, ref: reference
*P-value <0.05, **P-value <0.01

DISCUSSION

Nonadherence to treatment is one of many reasons for pharmacological treatment failure and seizure recurrence [20].AEDs nonadherence was assessed by an eight-item Morisky Medication Adherence Scale. Currently, therapeutic advances have resulted in meaningful changes in the diagnosis and management of epilepsy [21].

The present study showed that the prevalence of AEDs non-adherence was 63.1%. The present finding was in line with the study conducted in Addis Ababa 65.5%, Palestine 63.2%, Debre Berhan 41.3%, Gondar 17.6% [22, 23, 24, 25]. The similarity where in Ethiopia most epileptic patients interrupt their follow up due to they had no enough education about AEDs side effects, and drug interaction, so due to fear of adverse effects, and no brought them recovery from epilepsy instantly they discontinue their medication. And also on the contrary, our finding was higher than studies conducted Northwest Ethiopia 37.8%,Finland 34%[26,27].In our survey somewhat epileptic patients were eager to visit their follow up, and also somewhat education where given to them. Our finding was lower than study employed in Nigeria 85%, Brazil 71.1% [28, 29]. The difference in our country no strategy to manage epileptic patients during follow up, and the main reasons where epileptic patients were not treated by matured psychiatrists rather treated by physicians in our study.

The current study was revealed phenobarbital and carbamazepine was the mostly acquired from AEDs were similar with the study carried out in Yirgalem General Hospital [30] which revealed the majority of the participants were on phenobarbital and Carbamazepine combination therapy. This due to those drugs availability were high, and the patents where got them at hospitals or community pharmacies. Our survey displayed respondents who had got monthly income less than 1500 Ethiopian birr were similar with the survey carried out in Debre Berhan [24] which was revealed the study participants who earn less than 1000 Ethiopian birr were more likely to have unfavorable attitude than who earn greater than 3000 Ethiopian birr per month. The possible reason might be because having more monthly income is associated with higher in participants' willing to bought the medication even the medications where expensive, and drug expensiveness where the main reason for non-adherence of patients who had earn less monthly income.

Our study revealed the respondents who were get their AEDs out of pocket were (AOR: 4.021; 95%CI: 3.154-9.045; P=0.001) were 4 times more likely affect the AEDs adherence than those who got free where higher than the survey conveyed in Debre Markos Referral Hospital and Finote Selam District Hospital [26] which showed people with epilepsy who were buying AEDs were about 2.76 times more likely as to be non adherent as compared with those who were getting their AEDs free of charge. This was due to patients who got their medication out of pocket where sometimes cease to purchased their medications, and those who had get the medicine free were continue their medications in whatever circumstances. The current study displayed those respondents who had take AEDs for greater than 5 years (AOR:2.015; 95%CI: 0.698-2.436;P=0.004) were 2 times more likely to be non-adherent were less than the study conducted in Northwest Ethiopia[26] which showed that regarding duration of treatment, those people with epilepsy who were being on treatment for 6 years and above were 3.47 times more likely to be non-adherent as compared with participants who were on treatment for 3 months to 1 years. Due to long time of treatment, patients bored to take the medication because most of them had no enough knowledge on anti- epileptic medication effectiveness.

The present study revealed that regarding marital status divorced (AOR:3.215; 95%CI:1.413-2.493;P=0.001) were 3 times more likely have poor adherence than others category of marital status where in line with the convey surveyed in Yirgalem General Hospital [30]married patients had a higher level of adherence as compared to divorced and widowed patients. This was due to divorced women where most time stressed about their life, and their willing to act something in their life where decreased, so they don't taken the medication accordingly. The current study revealed that respondents who faced side effects of AEDs (AOR: 3.01; 95%CI: 1.927-7.026; P=0.001) were 3 times more likely affect AEDs adherence than who had no AEDs side effects were higher than the study employed in Debre Markos Referral Hospital and Finote Selam District Hospital [26] which showed that those participants who had AEDs side effect were 1.70 times more likely to be non-adherent as compared with those who had no AEDs side effect. In our survey majority of epileptic patients were interrupt their medication due to fear of side effects they after taken the medications.

CONCLUSION AND RECOMMENDATIONS

The prevalence of anti-epileptic drug nonadherence among patients with epilepsy was high. In our study, side effect of anti-epileptic drugs was the most common reason for non-adherence and regimen complexity was the least common reason. Age between twenty five up to forty four years old, divorced, educational status grade one up to eight, every two months follow up, duration of treatment greater than five years, purchasing medication out of pocket, presence of co-morbidity, side effects were significantly associated factors for anti- epileptic medication non-adherence. Epilepsy management programs maybe established by federal ministry of health, and communication strategies with the patients about their medication are necessary to improve adherence and to avoid the clinical consequences of poor adherence.

Acknowledgments

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Data Availability
The data used in this study can be obtained on written request to the corresponding author.