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ORIGINAL RESEARCH

Electrocardiogram Abnormalities and Associated Factors Among People with and without Epilepsy Attending the Outpatient Department at Referral Hospitals in Amhara Regional State, Northern Ethiopia, 2022: Institutional-Based Comparative Cross-Sectional Study

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Background: Epilepsy is a brain disease that is associated with electrocardiographic (ECG) abnormalities. However, this evidence is limited in Ethiopia. Studying ECG abnormality in epileptic patients could help minimize the cardiac problems and death of epileptic patients by early screening. This study was aimed to assess electrocardiogram abnormalities and associated factors among people with and without epilepsy at referral hospitals in Amhara Regional State (ARS), northern Ethiopia, 2022.

Methods: Institutional-based comparative cross-sectional study was conducted from April 20 to June 20, 2022. Three referral hospitals in ARS were selected by simple random sampling. Epileptic patients were selected by systematic random sampling, and 403 age- and sex-matched participants were selected from attendants of patients in the outpatient department. Interviewer-administered questionnaire and digital electrocardiograph were used for data collection. Data were entered to EpiData version 4.6 and exported to stata version 14 for analysis. Variables with P value <0.25 in bivariable analysis were entered to multivariable binary logistic regression. Strength of association was determined by adjusted odds ratio with a 95% confidence interval (CI).

Results: The prevalence of ECG abnormality was 40.0% (95% CI = 34.7–46.8) and 29.0% (95% CI = 23.2–34.3) in epileptic and non-epileptic subjects, respectively. The odds of ECG abnormality was 58% higher among epileptic patients. Divorce, duration of epilepsy, uncontrolled epilepsy, former/current smoker, adequate physical activity, hypertension, and overweight/obesity were associated with ECG abnormality among epileptic patients.

Conclusion and Recommendations: The proportion of ECG abnormality was higher among the epileptic than the non-epileptic group. This should be a wake-up call for stakeholders to establish appropriate measurements to reduce cardiac issues of epileptic patients.

Keywords: electrocardiographic abnormality, epilepsy, Ethiopia

Introduction

Epilepsy is a brain disease characterized by at least two seizures that occur 24 hours apart without precipitating factors.[1]

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Cardiovascular problems, the leading cause of mortality globally in the general population,[2] are significantly more common in epileptic patients than in non-epileptic individuals.[3] However, most patients remain asymptomatic until the occurrence of arrhythmia, myocardial infarction, and sudden cardiac arrest.[4] Since the traditional cardiac screening methods like age, diabetes status, hypertension, and smoking status could not fully identify cardiac problems,[5] electrocardiography remains the best method of early screening before severe cardiac disturbance and death.[6] The risk of sudden cardiac death increases three-fold in epileptic patients compared to non-epileptics due to an already existing increased risk of congenital or acquired heart disease among epileptic patients.[7]

Electrocardiographic abnormalities, which indicate problems in the heart or its vasculature, are common among epileptic patients.[8] The prevalence of abnormal electrocardiogram (ECG) finding in epileptic patients in the Caucasian population is 31.8%.[9] In India, 9.4% of epileptic patients had abnormal QTc intervals,[10] and in Egypt 51% of temporal lobe epileptic patients had prolonged QTc intervals.[11] Moreover, abnormalities in ECG among epileptic patients is associated with a higher risk of death.[10]

Electrocardiographic abnormalities in people with epilepsy are caused by depolarization and repolarization defects due to disruption of ion channels by anti-epileptic drugs (AEDs), myocardial ischemia due to prolonged contraction in repeated autonomic stimulation of the heart, and as a result of genetic mutation of ion channels found both in the brain and the heart.[12,13] These electrocardiographic changes are associated with age,[14] gender,[14] alcohol, cigarette smoking,[15] chat chewing,[16] overweight and/or obesity,[17] hypertension,[9] antiepileptic drugs (AEDs),[18] duration of epilepsy,[19] and frequency of seizure.[20]

The current epilepsy management is targeted mainly at symptomatic treatment with AEDs and fails to screen ECG abnormalities. Atenolol is effective in the management of long-standing cardiac electrical disturbances after seizure in animal studies.[21] However, to decrease cardiac issues neither atenolol nor any other intervention has been practised as part of epilepsy follow-up in Ethiopia. This is due to limited research-based evidence in this country. Even globally, previous studies were done either in small sample sizes, not based on matched age and sex groups, or did not show factors associated with ECG abnormality. Our study attempts to fill these gaps.

Electrocardiographic screening is a cost-effective and non-invasive method to decrease the risk of sudden unexpected death of epileptic patients by detecting cardiac repolarization and depolarization problems early.[22] This study is intended to evaluate the ECG abnormalities and associated factors in people with epilepsy and attendants of patients in outpatient departments in referral hospitals found in Amhara Regional State.

Objectives

General Objective

To assess the prevalence and factors associated with electrocardiogram abnormalities among people with and without epilepsy in the outpatient department at referral hospitals in Amhara Regional State, northern Ethiopia, 2022.

Specific Objectives

To compare the prevalence of electrocardiogram abnormality between epileptic and non-epileptic individuals in referral hospitals in Amhara Regional State, northern Ethiopia, 2022.

To determine the association between epilepsy and ECG abnormality among epileptic patients who attend outpatient follow-up and attendants of patients in outpatient departments at referral hospitals in Amhara Regional State, northern Ethiopia, 2022.

To identify factors associated with ECG abnormality among epileptic patients who attend outpatient follow-up at referral hospitals in Amhara Regional State, northern Ethiopia, 2022.

To establish factors associated with ECG abnormality among attendants of patients in outpatient departments at referral hospitals in Amhara Regional State, northern Ethiopia, 2022.

Materials and Methods

Study Setting, Design, and Period

This was an institutional-based comparative cross-sectional study conducted from April 20 to June 20, 2022 in referral hospitals found in Amhara Regional State (ARS). There are eight referral hospitals in the region, namely University of Gondar Comprehensive Specialized Referral Hospital, Tibebe Gion Comprehensive Referral Hospital, Felegehiwot Comprehensive Referral Hospital, Dessie, Woldia, Debre Markos, Debre Tabor, and Debre Birhan Referral Hospital. These hospitals have been serving about 2064 adult epileptic patients in the outpatient department. Of these, Debre Markos, Felegehiwot, and Dessie Referral Hospitals were the actual randomly selected study sites, which serve 364, 309, and 304 adult epileptic patients, respectively.

Felegehiwot Referral Hospital is found in Bahir Dar, the capital city of ARS. It is located 565 kilometers (km) northwest of Addis Ababa, the capital city of Ethiopia. It is currently serving 309 adult epileptic patients.

Dessie Referral Hospital is found in Dessie town in North Wollo Zone in Amhara Region. Dessie town is found 401 km northeast of Addis Ababa and 471 km from Bahir Dar. Debre Markos Referral Hospital is found at Debre Markos town located 256 km from Bahir Dar and 300 km from Addis Ababa.

Population and Eligibility Criteria

All epileptic patients aged 18 years or more and on follow-up at referral hospitals found in ARS were our source population, and those who visited follow-up clinic at selected hospitals during the study period were our study population for the epileptic group. The other source population for the second group was attendants of patients in the outpatient department at referral hospitals found in ARS. Those attendants of patients in outpatient departments at referral hospitals found in ARS during the study period were the second study population. For the first group, all epileptic patients aged 18 or more years who visited follow-up clinics, and for the second group, sex and age (within a range of 5 years with the first group) matched attendants aged 18 years or above who assisted outpatients at the selected hospitals during the study period were included in this study. However, patients with seizures within the day of data collection were excluded. Patients with lesions over the chest, hands, and feet were also excluded since electrodes were put around these areas which may irritate them, making them unable to be calm during the procedure, and also to decrease the risk of infection for the subsequent study subjects.

Sample Size Determination and Sampling Procedures

The sample size was determined in Epi Info-7 based on the prevalence of ECG abnormality in terms of QTc interval abnormality between epileptic (8.4%) and non-epileptic (2%) groups studied in Egypt.[20] Considering equal sample size, 95% confidence interval, and power of 80%, it yielded a sample size of 188 for each group.

Since staging exists in selecting hospitals, we used a design effect and multiplied each sample size by 2, giving 376. By Considering a 10% non-response rate, the required sample size was 414 for each group. Therefore, the total sample size was 828.

Three hospitals were selected by a simple random sampling method. These were Felegehiwot, Dessie, and Debre Markos referral hospitals. Through reading two months of the chronic follow-up logbook, we found that 309, 364, and 304 adult epileptic patients aged 18 years or above were having follow-up at Felegehiwot, Debre Markos, and Dessie comprehensive referral hospitals, respectively, during February and March 2022. These hospitals served a total of 977 adult epileptic patients. Proportionate allocation was done to select 414 samples in this population so that 131, 154, and 129 were the actual sample sizes, respectively, in these hospitals. Then, systematic random sampling was executed to select epileptic patients after the Kth interval, calculated as: K = total study population/sample size, and was found to be two. Lottery was drawn independently for the selected hospitals to select either one or two. In this way, number one for Felegehiwot and number two for Dessie and Debre Markos hospitals were drawn. Finally, using these numbers as a starting point in the order of patients card in the follow-up clinic, the next participants were selected every second interval until the required sample size was met.

Participants for the second (non-epileptic) group were selected among volunteers from attendants of patients in outpatient departments that absolutely matched for sex and within 5 years range in age with the epileptic group from each hospital.

Operational Definitions

Epileptic patient: any patient diagnosed with epilepsy and having follow-up in the respective referral hospital.

ECG abnormality: any deviation in wave, segment, or interval based on the Minnesota criteria.[23]

Defined daily dose for antiepileptic drugs: according to WHO, an average dose of the drug that should be taken per day to attain maintenance for adults with the main indication,[24] which is as follows: carbamazepine = 1000 mg, clonazepam = 8 mg, ethosuxamide = 1250 mg, phenobarbital = 100 mg, phenytoin = 300 mg, pyrimidine = 1250 mg, lamotrigine = 300 mg, valproate = 1500 mg.[25]

Combination therapy: consumption of more than one AED per day.[8]

Uncontrolled epilepsy: if there is seizure within the last six months despite treatment with AEDs.[26]

Adequate physical activity: according to CDC criteria, having a brisk walk for 150–300 minutes, or running/ jogging 75–150 minutes, or any muscle strengthening activity of at least two times per week.[27]

Smoking status: current smoker, a person who smoked at least 100 cigarettes in his/her life time and currently smoking; former smoker, a person who smoked 100 or more cigarettes but not currently; never smoker, a person who has smoked less than 100 cigarettes or not at all.[28]

Current chat chewer: a person who chewed chat in the last three months of data collection; ever chat chewer, at least once in a life time; non-chewer, no history of any chat chewing.[29]

Hypertension: a systolic and/or diastolic blood pressure of ≥140 mmHg and ≥90 mmHg, respectively, or being on anti-hypertensive drugs.[30]

Alcohol consumption: frequent drinker, more than three times per week; moderate drinker, three or less times per week; and abstainer, none at all.[31]

Weight: underweight, BMI <18.5 kg/m^2; normal, BMI 18.5–24.9 kg/m^2; overweight, BMI 25–29.9 kg/m^2; and obese, BMI ≥30 kg/m^2.[32]

Data Collection Instruments and Procedures

An interviewer-administered structured questionnaire was used to collect sociodemographic, behavioural, and clinical factors considering the WHO stepwise approach for surveillance.[33] Secondary data were also used to collect drug-related data. Mercury sphygmomanometer, weight balance, and height measuring board were used to measure blood pressure, weight, and height, respectively. A digital electrocardiograph was used to measure electrocardiographic parameters.

Epileptic patients' data were collected from those who fulfil the inclusion criteria. Sociodemographic, behavioural, and clinical information, as well as height and weight measurement were collected by three trained clinical nurses. First, blood pressure was measured by mercury sphygmomanometer according to the WHO guideline.[34]

Then, height and weight were measured according to the WHO guideline.[34] Body mass index was calculated as weight in kilogram divided by height squared in meter in STATA. Then, data of the sex- and age-matched (maximum of five years above or below the age of each epileptic group) non-epileptic group were collected.

Next, sociodemographic, behavioural, and clinical factors were collected. Lastly, electrocardiography was done by three experts of the respective hospital using a 12-lead digital electrocardiograph with a paper speed of 25 mm per second. A paper horizontally calibrated with large boxes representing 0.2 seconds, divided into 5 small boxes that represent 0.04 seconds and vertically with 10 mm representing 1 millivolt was used. The study participant was made to resume supine position, 45 degrees tilted upward, after having removed his/her clothes over the chest, bracelets, and any other electromagnetic substances from his/her body. Then 10 electrodes, 4 on each forearm and legs and 6 on the chest were applied. After completing the required data from individuals, a mark which says “ECG”, followed by signature of the data collector, was signed from epileptic patients to avoid duplication in their next follow-up. For the non-epileptic group, they were orally informed not to be part of this study within the next two months.

Data Quality Control

The questionnaire was prepared in English version and translated to Amharic version by a language expert. Then this was again translated back to English version by another language expert to check for consistency. Data collectors were trained for a day about the purpose of the research, the ethical issues, the questionnaire, and the measurement procedures. Pre-test was done among 10 epileptic and seven non-epileptic subjects at Woldia referral hospital. Sociodemographic, behavioural, and clinical data were collected under close supervision by supervisors in each hospital. Electrocardiography was done by three experts of the hospital. Electrocardiographic parameters were interpreted by a senior cardiologist. The cardiologist was allowed to interpret the cardiogram only without knowing the epileptic status of the study participant.

Study Variables

Dependent Variable

Electrocardiogram abnormality (Yes/ No).

Independent Variables

Sociodemographic variables: age, sex, marital status, residence, educational status, occupation, and income.

Behavioural Variables

Alcohol, smoking, chat chewing, and physical activity.

Clinical Variables

Epilepsy, body mass index, hypertension, and for the epileptic group (duration of epilepsy, type of drug for the disease, frequency of seizure in the last 3 months, epilepsy control, and the ratio of prescribed daily dose to defined daily dose).

Data Processing and Analysis

The collected data were checked for completeness and entered into EpiData version 4.6 and exported to stata-14 for analysis. Normality of continuous independent variables was checked by histogram. Median ± interquartile range (IQR) was used for descriptive statistics for variables with no normal distribution. The epileptic and non-epileptic groups were compared based on their sociodemographic, behavioural, and clinical factors (hypertension and BMI) to check whether they are different populations or not. Wilcoxon rank sum test was used to compare continuous variables without normal distribution. These groups were considered different when the P value was ≤ 0.05. Two groups proportion test and X^2-test were applied to compare the magnitude of ECG abnormality between groups. The association between ECG abnormality and epilepsy was checked by chi-square test statistics.

Binary logistic regression was executed three times. The first regression was done in all 806 study participants to determine the strength of association between ECG abnormality and epilepsy. The mean and individual variance inflation factor as well as the Hosmer–Lemeshow goodness of fit were done. Crude odds ratio of variables was determined in bivariable logistic regression. Then, those with P value less than 0.25 were entered to multivariate binary logistic regression to check the factors associated with ECG abnormality among all study participants. Decision of association was done at P value ≤ 0.05. Strength of association was expressed in adjusted odds ratio with 95% confidence interval. The same procedure was done for the next two models. The second regression was done to determine factors associated with ECG abnormality among non-epileptic patients. Finally, binary logistic regression was done to determine the factors associated with ECG abnormality among epileptic patients.

Results

Sociodemographic Characteristics of Study Participants

In this study, a total of 403 epileptic and 403 non-epileptic study subjects were recruited, with a response rate of 97.3% for each group. There was no statistically significant difference between these two groups of study participants in their sociodemographic characteristics (Table 1).

Table 1 Sociodemographic Status of Epileptic and Non-Epileptic Groups in ARS Referral Hospitals, Ethiopia, 2022

Variables	Categories	Group Frequency, *N* (%)		*P* value
		Epileptic	Non-Epileptic	
Age, median (IQR)		28 (11)	25 (8)	0.35
Marital status	Married	154 (38.2)	184 (46.7)	0.39
	Unmarried	207 (51.4)	189 (46.9)	
	Divorced	30 (7.4)	21 (5.2)	
	Widowed	12 (3.0)	9 (2.2)	
Residence	Urban	81 (20.1)	77 (19.1)	0.80
	Rural	322 (79.9)	326 (80.9)	
Income, median (IQR)		2000 (2000)	2000 (1400)	0.94
Educational status	Unable to read/ write	97 (24.1)	95 (23.6)	0.10
	≤Grade 8	98 (24.3)	85 (21.1)	
	Grade 9–12	125 (31.0)	113 (28.0)	
	Diploma or above	83 (20.6)	110 (27.3)	
Occupation	Farmer	119 (29.5)	125 (31.0)	0.47
	Student	121 (30.0)	115 (28.5)	
	Government employee	39 (9.7)	46 (11.4)	
	Merchant	20 (5.0)	30 (7.5)	
	Daily labourer	42 (10.4)	31 (7.7)	
	House wife	12 (3.0)	12 (3.0)	
	Private employee	29 (7.2)	25 (6.2)	
	Other	21 (5.2)	19 (4.7)	

Note: Other (pensioner, prisoner, driver).
Abbreviation: IQR, interquartile range.

The median age of epileptic and non-epileptic subjects was 28±(IQR 11) and 25±(IQR 8) years, respectively (*P* value in the Wilcoxon rank sum test = 0.35). The age of epileptic patients ranges from 18 to 53 years, and it was 18 to 54 years in the non-epileptic group. In each group, 214 (53.1%) of the study participants were males.

The median monthly personal income of epileptic participants was 2000±(IQR 2000) Ethiopian birr, with minimum and maximum of 200 and 10,000 Ethiopian birr, respectively. The median monthly income of the non-epileptic participants was 2000±(IQR 1400) Ethiopian birr, with minimum and maximum of 600 and 11,000 Ethiopian birr, respectively (Table 1).

Behavioural Characteristics of Study Participants

Epileptic patients were more frequently chat chewers and smokers than were non-epileptic subjects. About 7.9% of epileptic and 4.9% of non-epileptic participants were either former or current smokers. Similarly, 16.6% of epileptic and 12.9% of non-epileptic subjects had history of either ever or current chat chewing. There was no significant difference between them in status of physical activity and alcohol drinking (Table 2).

Table 2 Comparison of Behavioural Factors Between Epileptic and Non-Epileptic Subjects in ARS, Ethiopia, 2022

Variable	Category	Group, Total (%)		*P* value
		Epileptic	Non-Epileptic	
Smoking	Never	371 (92.1)	383 (95.1)	0.01*
	Former/current	32 (7.9)	20 (4.9)	
Chat chewing	Never	336 (83.4)	351 (87.1)	0.047*
	Ever/current	67 (16.6)	52 (12.9)	
Alcohol drinking	Abstainer	30 (7.4)	34 (8.5)	0.26
	Moderate	274 (68.0)	288 (71.5)	
	Frequent	99 (24.6)	81 (20.0)	
Physical activity	Adequate	142 (35.2)	161 (40.0)	0.47
	Inadequate	261 (64.8)	242 (60.0)	

Note: **P* value ≤0.05.

Clinical Profile of Study Participants

About 8.4% and 7.4% of epileptic and non-epileptic groups, respectively, were hypertensive (*P* value = 0.09). More than half (58.8%) of hypertensive epileptic patients and nearly half (50.7%) of hypertensive non-epileptic subjects had ECG abnormality. In addition, there was no significant difference between these groups in BMI (*P* value = 0.31). Nearly 7.4% and 9.4% of epileptic and non-epileptic subjects, respectively, were either overweight or obese. In the epileptic group, 56.7% of overweight/obese people had ECG abnormality; in the non-epileptic group, 56.9% of overweight/obese people had the condition.

The median duration of illness with epilepsy was 9±(IQR 7) years. The median duration of epilepsy among those with and without ECG abnormality was 10±7 and 8±6, respectively (*P* = 0.013). More than half (61.0%) of them were having combined drug therapy (Table 3).

Table 3 Clinical Profile of Non-Epileptic and Epileptic Patients at ARS Referral Hospitals, Ethiopia, 2022

Variable	Category	Total (%)	ECG Abnormality		X^2/ Wilcoxon (*P* value)
			Yes in %	No in %	
Epileptic group					
Hypertension	Yes	34 (8.4)	58.8	41.2	0.002*
	No	369 (91.6)	32.5	67.5	
BMI	Underweight	12 (3.0)	50.0	50.0	0.003*
	Normal	361 (89.6)	33.1	66.9	
	Overweight/ obese	30 (7.4)	56.7	43.3	
Duration of epilepsy, median ±IQR (years)		9±7	10±7	8±6	0.013*
Epilepsy control	Controlled	286 (81.0)	31.0	69.0	<0.001*
	Uncontrolled	117 (29.0)	62.1	31.9	

(*Continued*)

Table 3 (Continued).

Variable	Category	Total (%)	ECG Abnormality		X^2/ Wilcoxon (*P* value)
			Yes in %	No in %	
Type of AED	Carbamazepine	66 (16.4)	43.2	56.8	0.735
	Phenobarbital	73 (18.1)	42.9	57.1	
	Others	18 (4.5)	34.6	65.4	
	Combined	246 (61.0)	40.3	59.7	
PDD to DDD ratio	<One	280 (69.5)	38.9	61.1	0.245
	One	123 (30.5)	43.3	56.7	
Seizure within 3 months	None	336 (83.3)	37.5	62.5	0.005*
	One	39 (9.7)	44.7	55.3	
	>One	28 (7.0)	52.4	47.6	
Non-epileptic group					
Hypertension	Yes	30 (7.4)	50.7	49.3	0.03*
	No	373 (92.6)	31.9	68.1	
BMI	Underweight	8 (2.0)	25	75	0.01*
	Normal	357 (88.6)	35.1	64.9	
	Overweight/ obese	38 (9.4)	56.9	42.1	

Note: *P value ≤0.05.
Abbreviations: IQR, interquartile range; BMI, body mass index; AED, anti-epileptic drug; PDD, prescribed daily dose; DDD, defined daily dose.

Comparison of ECG Abnormality Among the Epileptic and the Non-Epileptic Group

Among all study participants, 34.5% (95% CI = 30–39.3%) were having at least one pattern of ECG abnormality.

The prevalence of ECG abnormality was 40.0% (95% CI = 34.7–46.8%) among the epileptic group, while it was about 29.0% (CI = 23.2–34.3%) in the non-epileptic group. The magnitude of ECG abnormality among female epileptic patients was 43.75%, while it was 27.6% among non-epileptic study participants ($P = 0.0358$). In males, the prevalence of ECG abnormality was 36.3% and 29.9% in the epileptic and non-epileptic group, respectively ($P = 0.244$).

In particular, abnormal Q wave (8.9% of epileptic and 2.5% of non-epileptic group, $P = 0.005$) and BBB (7.4% of epileptic and 2% of non-epileptic group, $P = 0.01$) were significantly more prevalent in the epileptic group than in the non-epileptic group. Abnormal QTc accounted for 3.5% and 1.5% in the epileptic and non-epileptic group ($P = 0.042$). Similarly, 3.5% and 1.2% of the epileptic and the non-epileptic group, respectively, had abnormal ST segment ($P = 0.040$). The most frequently observed ECG abnormalities were axis deviation (epileptic 10.4%, non-epileptic 8.9%) and abnormal heart rate (epileptic 10.4%; non-epileptic 7.4%) (Table 4).

Association of Epilepsy with ECG Abnormality

Regression was done in the total study participants (for the 806 study participants). Epilepsy (yes/no) was considered as one of the determinants. Being epileptic was positively associated with ECG abnormality (x^2, $P = 0.022$, COR = 1.63, 95% CI = 1.07–2.45). After the effect of smoking, physical exercise, hypertension, and BMI had been adjusted, the odds of ECG abnormality was 58% higher among people with epilepsy than without epilepsy (AOR 1.01–2.48). Being former/current smoker (AOR = 3.06, 95% CI = 1.71–5.59), having adequate physical activity (AOR = 0.4, 95% CI = 0.09–0.89), being overweight/obese (AOR = 3.16, 95% CI = 1.99–5.72), and having hypertension (AOR = 3.48, 95% CI = 1.02–6.37) were associated with ECG abnormality (Table 5).

Table 4 Patterns of ECG Abnormality Among the Epileptic and the Non-Epileptic Group in ARS Referral Hospitals, Ethiopia, 2022

Variable	Category	Total Number (%)	Groups in Number (%)		*P* value
			Epileptic	Non-Epileptic	
ECG abnormality	Yes	278 (34.5)	161 (40.0)	117 (29.0)	0.022*
	No	528 (65.5)	242 (60.0)	286 (71.0)	
Heart rate	Normal	734 (91.1)	361 (89.6)	373 (92.6)	0.295
	Abnormal	72 (8.9)	42 (10.4)	30 (7.4)	
P wave	Normal	786 (97.5)	394 (97.8)	392 (97.3)	0.461
	Abnormal	20 (2.5)	9 (2.2)	11 (2.7)	
PR interval	Normal	787 (97.6)	391 (97)	396 (98.3)	0.053
	Abnormal	19 (2.4)	12 (3.0)	7 (1.7)	
QRS wave	Normal	781 (96.9)	388 (96.3)	393 (97.5)	0.398
	Abnormal	25 (3.1)	15 (3.7)	10 (2.5)	
QTc interval	Normal	786 (97.5)	389 (96.5)	397 (98.5)	0.042
	Abnormal	20 (2.5)	14 (3.5)	6 (1.5)	
BBB (R/L)	Yes	38 (4.7)	30 (7.4)	8 (2.0)	0.01*
	No	768 (95.3)	373 (92.6)	395 (98.0)	
Axis deviation	Yes	78 (9.7)	42 (10.4)	36 (8.9)	0.613
	No	728 (90.3)	361 (89.6)	367 (91.1)	
Right/left atrial hypertrophy	Yes	24 (3.0)	10 (2.5)	14 (3.5)	0.703
	No	782 (97.0)	393 (97.5)	389 (96.5)	
Right ventricular hypertrophy	Yes	20 (2.5)	12 (3.0)	8 (2.0)	0.522
	No	786 (97.5)	391 (97.0)	395 (98.0)	
Left ventricular hypertrophy	Yes	31 (3.8)	14 (3.5)	17 (4.0)	0.610
	No	775 (96.2)	389 (96.5)	386 (96.0)	
Abnormal Q wave	Yes	46 (5.7)	36 (8.9)	10 (2.5)	0.005*
	No	760 (94.3)	367 (91.1)	393 (97.5)	
Abnormal T wave	Yes	28 (3.5)	20 (5.0)	8 (2.0)	0.103
	No	778 (96.5)	383 (95.0)	395 (98.0)	
Abnormal ST segment	Yes	19 (2.4)	14 (3.5)	5 (1.2)	0.040
	No	787 (97.6)	389 (96.5)	398 (98.8)	

Notes: *P value ≤0.05.
Abbreviation: BBB (R/L), right and/or left bundle branch block.

Factors Associated with ECG Abnormality Among Epileptic Patients

The association of ECG abnormality with age, sex, residence, marital status, education, occupation, income, physical activity, smoking status, chat chewing, BMI, hypertension, duration of disease, treatment outcome, type of AED, PDD to DDD ratio, and number of seizures in the last three months was checked in bivariate binary logistic analysis. Residence, marital status,

Table 5 Factors Associated with ECG Abnormality Among Non-Epileptic and Epileptic Patients in ARS Referral Hospitals, Ethiopia, 2022

Variables	ECG Abnormality (*N* = 806)		COR (95% CI)	AOR (95% CI)
	Yes	No		
Age (median ± IQR)	27 ± 9	26 ± 9	2.01 (0.76–3.24)	1.95 (0.74–3.02)
Residence				
Urban	56	102	1	1
Rural	222	426	0.95 (0.22–1.340)	0.38 (0.18–1.04)
Marital status				
Married	110	228	1	1
Unmarried	132	264	1.04 (0.51–1.92)	1.01 (0.63–2.04)
Divorced	27	24	2.33 (1.29–4.33)	1.24 (0.97–3.91)
Widowed	9	12	1.55 (0.21–2.35)	1.14 (0.48–2.12)
Smoking				
Never smoker	243	511	1	1
Former/current	35	17	4.33 (1.80–6.01)	3.06 (1.71–5.59)
Chat chewing				
Never	225	462	1	1
Ever/current	53	66	1.65 (0.51–2.58)	1.58 (0.39–2.13)
Physical activity				
Adequate	77	226	0.51 (0.19–0.91)	0.4 (0.09–0.89)
Inadequate	201	302	1	1
Epilepsy				
Yes	161	242	1.63 (1.07–2.45)	1.58 (1.01–2.48)
No	117	286	1	1
BMI				
Underweight	9	11	1.07 (0.52–2,99)	1.01 (0.95–2.60)
Normal	224	494	1	1
Overweight/ obese	45	23	4.31 (2.09–7.02)	3.16 (1.99–5.72)
Hypertension				
Yes	44	20	4.78 (2.56–7.06)	3.48 (2.02–6.37)
No	234	508	1	1

Abbreviations: IQR, interquartile range; *N*, total number of participants (epileptic and non-epileptic).

educational status, physical activity, sex, chat chewing, smoking, BMI, hypertension, duration of illness, status of seizure control, PDD to DDD ratio, and number of seizures in the last three months had significant association with ECG abnormality in COR at *P* value less than 0.25. Marital status, physical activity, smoking, hypertension, BMI, and disease-specific factors (uncontrolled epilepsy and duration of epilepsy) had statistically significant association with ECG abnormality in multivariate

analysis. Being divorced (AOR = 2.39, 95% CI = 1.04–6.96), duration of epilepsy (AOR = 1.15, 95% CI = 1.05–1.27), uncontrolled seizure (AOR = 3.64, 95% CI = 1.57–5.86), being a former/current smoker (AOR = 4.66, 95% CI = 2.89–6.68), adequate physical activity (AOR = 0.6, 95% CI = 0.12–0.91), being hypertensive (AOR = 5.41, 95% CI = 2.82–9.31), and overweight/obesity (AOR = 3.11, 95% CI = 2.14–4.96) were associated with ECG abnormality (Table 6).

Table 6 Factors Associated with ECG Abnormality Among Epileptic Patients at ARS Referral Hospitals, Ethiopia, 2022

Variables	ECG Abnormality (*N* = 403)		COR (95% CI)	AOR (95% CI)
	Yes	No		
Residence				
Urban	38	43	1	1
Rural	123	199	0.70 (0.32–1.26)	0.51 (0.22–1.08)
Marital status				
Married	58	96	1	1
Unmarried	76	131	0.96 (0.51–1.72)	1.36 (0.49–1.34)
Divorced	21	9	3.86 (1.33–6.63)	2.39 (1.04–6.96)
Widowed	6	6	1.66 (0.31–4.75)	1.46 (0.40–3.14)
Educational status				
Unable to read/ write	39	58	1	1
≤Grade 8	41	57	1.07 (0.54–2.38)	1.01 (0.42–1.63)
Grade 8–12	49	76	0.96 (0.52–1.73)	0.72 (0.25–1.52)
Diploma and above	32	51	0.63 (0.34–1.67)	0.60 (0.34–1.36)
Chat chewing				
Never	128	208	1	1
Ever/current	33	34	1.58 (0.42–2.59)	1.04 (0.35–1.93)
Smoking				
Never smoker	137	234	1	1
Former/current	24	8	5.12 (3.11–7.72)	4.66 (2.89–6.68)
Physical activity				
Adequate	46	96	0.61 (0.14–0.97)	0.60 (0.12–0.91)
Inadequate	115	146	1	1
BMI				
Underweight	6	6	1.69 (0.44–2.75)	1.41 (0.35–2.63)
Normal	134	227	1	1
Overweight/ obese	21	9	3.95 (2.29–5.02)	3.11 (2.14–4.96)

(*Continued*)

Table 6 (Continued).

Variables	ECG Abnormality (*N* = 403)		COR (95% CI)	AOR (95% CI)
	Yes	No		
Hypertension				
Yes	26	8	5.63 (2.92–9.01)	5.41 (2.82–9.31)
No	135	234	1	1
Duration of epilepsy (median±IQR)	10±7	8±6	1.99 (1.22–2.27)	1.15 (1.05–1.27)
Epilepsy control				
Controlled	90	196	1	1
Uncontrolled	71	46	3.36 (1.83–6.47)	3.64 (1.57–5.86)
PDD to DDD ratio				
<One	103	177	1	1
=One	58	65	1.53 (0.77–2.19)	1.19 (0.64–1.90)
Number of seizures in the last 3 months				
None	130	206	1	1
One	17	22	1.22 (0.38–2.96)	1.02 (0.31–2.35)
>One	14	14	1.58 (0.80–3.05)	1.22 (0.23–5.97)

Abbreviations: IQR, interquartile range; *N*, total number of epileptic participants.

Factors Associated with ECG Abnormality Among the Non-Epileptic Group

In the non-epileptic group, age, sex, marital status, smoking, chat chewing, physical activity, BMI, and hypertension were associated with ECG abnormality in bivariate analysis at *P* value less than 0.25. From these, former/current smoking (AOR = 1.09, 95% CI = 1.03–2.09), adequate physical activity (AOR = 0.23, 95% CI = 0.01–0.68), overweight/obesity (AOR = 3.00, 95% CI = 1.01–5.04), and hypertension (AOR = 2.99, 95% CI = 1.94–5.03) were factors associated with ECG abnormality in multivariate analysis (Table 7).

Table 7 Factors Associated with ECG Abnormality Among Outpatient Attendants of ARS Referral Hospitals, Ethiopia, 2022

Variables	ECG Abnormality (*N* = 403)		COR (95% CI)	AOR (95% CI)
	Yes	No		
Age (median± IQR)	23±8	28±9	2.01 (0.76–3.24)	1.95 (0.74–3.02)
Sex				
Male	64	150	1	1
Female	53	139	0.89 (0.46–1.72)	0.87 (0.43–1.69)
Marital status				
Married	52	132	1	1
Unmarried	56	133	1.07 (0.49–1.74)	1.03 (0.53–1.84)
Divorced	6	15	1.02 (0.77–1.73)	1.08 (0.66–1.91)
Widowed	3	6	1.27 (0.32–2.35)	1.25 (0.35–2.22)

(*Continued*)

Table 7 (Continued).

Variables	ECG Abnormality (*N* = 403)		COR (95% CI)	AOR (95% CI)
	Yes	No		
Smoking				
Never smoker	106	277	1	1
Former/current	11	9	3.19 (1.40–5.11)	1.09 (1.03–2.09)
Chat chewing				
Never	97	254	1	1
Ever/current	20	32	1.64 (0.71–3.01)	1.11 (0.21–2.99)
Physical activity				
Adequate	31	130	0.43 (0.02–0.71)	0.23 (0.01–0.68)
Inadequate	86	156	1	1
BMI				
Underweight	3	5	1.78 (0.32–2,18)	1.15 (0.81–2.14)
Normal	90	267	1	1
Overweight/ obese	24	14	5.10 (2.02–6.91)	3.00 (1.04–5.04)
Hypertension				
Yes	18	12	4.15 (1.96–6.01)	2.99 (1.94–5.03)
No	99	274	1	1

Abbreviations: IQR, interquartile range; *N*, total number of non-epileptic participants.

Discussion

The aim of the current study was to determine the prevalence and associated factors of ECG abnormality for epileptic patients and non-epileptic attendants of patients in outpatient departments.

In this study, 34.5% of the total study participants had at least one pattern of ECG abnormality which was comparable with a study done in Caucasian population, 31.8%.[9] About 8.9% of them had abnormal heart rate (bradycardia or tachycardia), which is higher than a study conducted in China.[35] This may be due to the difference in sociodemographic characteristics between the two populations.[8] The proportion with abnormal Q wave in this study was 5.7%. This result is higher than the studies from Spain (3.5%),[36] China (1.28%),[35] and Angola (0.71%).[15] This may be because half of the study participants in the current study were epileptic patients which may raise the proportion of Q wave abnormality. This study revealed that 3.8% of study participants had left ventricular hypertrophy. This was consistent with a study in Spain, 3.2%.[36]

The proportion of overall ECG abnormality in epileptic patients, 40.0% (95% CI = 34.7–46.8%), was significantly higher than in the non-epileptic group, 29.0% (95% CI = 23.2–34.3%). This could be an indicator of the higher prevalence of unnoticed cardiovascular risks in epileptic patients.[8] Therefore, epileptic patients are more likely to experience sudden unexpected death.[3] Exceptionally, the proportions with BBB and abnormal Q wave, QTc, and ST segment were higher in epileptic patients than non-epileptic subjects. This result is in line with a global systematic review which found a higher proportion of pathologic Q wave in epileptic patients than in non-epileptic individuals.[37] This may signify higher occurrence of previous myocardial ischemia in epileptic patients.[38] The proportion was more specifically higher among female epileptic patients. This higher proportion of ECG abnormality in female epileptic patients may be as a result of interaction between AEDs and female hormones.[39] Anti-epileptic drugs increase the metabolism of female

sex hormones[40] and production of female sex hormone binding globulins,[41] which decreases the bioavailability of these hormones in blood. Therefore, the cardiovascular health-promoting effect of female sex hormones is decreased, leading to the increased risk of heart disease among female epileptic patients.[42] The other reason for the higher proportion of ECG abnormality among epileptic patients could be the effect of smoking. As indicated in the results section, the proportion of smokers among epileptic patients, 7.9%, was higher than in the non-epileptic group, 4.9% ($P = 0.04$). Again, the present study indicated that smoking was associated with ECG abnormality that could increase the magnitude of ECG abnormality in epileptic patients.

While a study conducted in the Netherlands found higher heart rate abnormality of epileptic patients than in controls,[8] the finding of this study revealed no difference in heart rate. This may be due to the fact that the Netherlands study might not have matching of groups based on age, sex, and other sociodemographic status, which our study did.

Factors associated with ECG abnormality among the whole group of 806 study participants were determined. Being epileptic, former/current smoker, adequate physical activity, overweight and/or obesity, and hypertension were associated with ECG abnormality. The odds of ECG abnormality among epileptic patients was 58% higher than the odds of ECG abnormality in the non-epileptic group (AOR = 1.58, 95% CI = 1.01–2.48). This may be due to the effect of genetic or seizure-induced changes to structure, autonomic function, and ion channels of the heart.[12,13] The focus of epilepsy may arise from the area of the brain that controls the activity of the heart. During seizure stimulation, it may therefore suppress or overactivate the heart.[13] Sometimes, the focus of seizure may also be on cortical areas that directly control autonomic nervous system, and firing of these areas cause undesired stimulation of autonomic nerves which affect the heart.[43] The effect of AEDs could also be responsible for the ECG abnormality by blocking ion channels of the heart.[44] Furthermore, congenital or acquired channelopathies that are found both in the heart and brain may be responsible for the mutual occurrence of epilepsy and ECG abnormality.[45]

Smoking was associated with ECG abnormality among the whole group of study participants, the epileptic group and the non-epileptic group. From total participants, the odds of ECG abnormality among smokers was 3.06 times (AOR 3.06, 95% CI = 1.71–5.59) higher than among non-smokers. This finding was supported by a study in Angola.[15] The harmful components of cigarette smoke like nicotine may be responsible for this difference. Nicotine is capable of altering the normal function of inward and delayed rectifier potassium channels, channels important for excitability and maintenance of membrane potential stability.[46] In another way, components of cigarette increase endogenous release of free radicals, decrease oxygen availability to the heart, favour inflammation and deposition of atherosclerotic plaque in coronary arteries, and finally lead to myocardial infarction.[47,48] Moreover, in the present study, the strength of association between former/current smoking and ECG abnormality was higher in the epileptic group (AOR = 4.66, 95% CI = 2.89–6.68) than in the non-epileptic group (AOR = 1.09, 95% CI = 1.03–2.09). This may be due to increased sympathetic activity due to smoking and therefore increase the severity of epilepsy,[49] which was associated with ECG abnormality in our study. In addition, both smoking and anti-epileptic drugs may have a synergistic effect for ECG abnormality by increasing the blood level of low-density lipoproteins and atherosclerosis.[50]

The other factor that was significantly associated with ECG abnormality in both the epileptic and the non-epileptic group was adequate physical activity. The odds of ECG abnormality was 40% in the epileptic group (AOR = 0.6, 95% CI = 0.12–0.91) and 90% in the non-epileptic group (AOR = 0.23, 95% CI = 0.01–0.68) lower among those with adequate physical activity than non-adequate physical activity. This may be due to the effect of physical activity in decreasing the risk factors of cardiac problems like dyslipidaemia, obesity, and insulin resistance.[51]

Among the 806 participants, being overweight and/or obese was associated with 3.16 times (AOR = 3.16, 95% CI = 1.99–5.72) higher odds of ECG abnormality than being of normal weight. Being overweight or obese was also associated with ECG abnormality in epileptic and non-epileptic groups separately. The strength of association between overweight/obesity and ECG abnormality was comparable in the epileptic and non-epileptic group (AOR = 3.11 versus 3.00). Among the epileptic group, the odds of ECG abnormality in overweight and/or obese subjects was 3.11 times (AOR = 3.11, 95% CI = 1.14–4.96) higher than among those with normal BMI. The odds of ECG abnormality was three times (AOR = 3.00, 95% CI = 1.04–5.04) higher than among normal BMI subjects in the non-epileptic group. First, accumulation of fat in the viscera of those people may physically displace the structure of the heart, so that the electrical axis is changed.[52] Second,

overweight/obesity is associated with metabolic alterations like dyslipidaemia and the associated immune response of hyperlipidaemia.[53]

Besides, hypertension was associated with ECG abnormality. Among the whole group of study participants, the odds of ECG abnormality among people with hypertension was 3.48 times (AOR = 3.48, 95% CI = 2.02–6.37) higher than among those without hypertension. This finding was consistent with the result of previous studies from Spain,[36] Caucasian population,[9] and Angola.[15] Hypertension could be associated with ECG abnormality due to functional or structural changes.[54] Structural remodelling of the heart to compensate the load of increased blood pressure triggers replacement of ion channels and dysfunction of gap junctions.[55]

Being divorced was significantly associated with ECG abnormality among epileptic patients only. The odds of having ECG abnormality was 2.39 (AOR = 2.39, 95% CI = 1.04–6.96) times higher among divorced epileptic patients than among married epileptic patients. Being divorced and epileptic could be related with heart problems by its psychosocial implications. Psychological problems lead to excessive secretions of cortisol which is complicated by dyslipidaemia, insulin resistance, and catecholamine hypersensitivity, finally resulting in damage of the cardiovascular system.[56]

A one-unit increase in the duration of epilepsy increased the odds of having ECG abnormality by 15% (AOR = 1.15, 95% CI = 1.05–1.27). This result was supported by a study done in Iran which indicated an increased risk of one of the components of ECG abnormality, the QRS wave, when duration of epilepsy increased.[19] This condition could be a result of prolonged exposure of the heart to AEDs which block ion channels of the heart or increase existence of cardiovascular risks like dyslipidaemia and insulin resistance.[12,39]

The odds of ECG abnormality among epileptic patients with uncontrolled seizure were 3.64 (AOR = 3.64 with 95% CI = 1.57–5.86) times higher than the odds of ECG abnormality among epileptic patients with controlled seizure. This evidence was supported by a study done in Egypt in which patterns of ECG abnormality were associated with uncontrolled epilepsy.[20] This could occur due to repetitive sympathetic stimulation of the heart during repetitive seizure.[12] Therefore, the heart contracts strongly to accomplish its duty. Due to severe muscular contraction, the vasculatures of the heart could be ischemic and the electrical bundles of the heart damaged. The other reason could be an uncontrolled surge of catecholamines that damage the heart during seizure activity.[57]

Strength and Limitation of the Study

This study has some strengths and limitations. Its strength was that the study was conducted in a multi-centre setting, which is more representative of the study population. Second, since it is a comparative study, it tells us the extent of ECG abnormality between epileptic and non-epileptic study participants.

The limitations of this study were, first, that study participants did not undergo laboratory screening for thyroid function test, random blood sugar, lipid profile, electrolyte level, complete blood count, and organ function tests. Therefore, such undiagnosed problems could be more likely in either group and thus could disrupt the findings. Second, the study failed to address those epileptic patients who did not start AED treatment. Therefore, ECG abnormalities were not compared between those who did or did not take AEDs.

Conclusion

The prevalence of ECG abnormality was higher in the epileptic group than in the non-epileptic group. Among patterns of ECG abnormality, BBB, abnormal QTc, ST segment, and Q wave were more common in the epileptic group. From the whole group of study participants, former or current smoking, overweight or obesity, hypertension, and epilepsy were factors that increase the odds of ECG abnormality, whereas adequate physical activity was associated with a decrease in the odds of ECG abnormality. Among the factors, hypertension and former or current smoking were more strongly associated with ECG abnormality in the epileptic group than in the non-epileptic group. Furthermore, being divorced, having a longer duration of epilepsy and uncontrolled epilepsy were associated with ECG abnormality among the epileptic group.

Recommendations

Policy makers are expected to design a strategy considering cardiovascular health assessment of epileptic patients for early detection of cardiac issues.

The government authorities are suggested to lead smoking cessation campaign.

Future studies are recommended to match study participants with body mass index and smoking status.

Health care providers need to pay attention to epileptic patients by full cardiovascular examination for earlier detection of cardiovascular problems.

Furthermore, epileptic patients as well as the general population are advised to establish cardiovascular health-promoting practices like physical exercise.

Abbreviations

AED, antiepileptic drug; ARS, Amhara Regional State; BBB, bundle branch block; BMI, body mass index; CI, confidence interval; DDD, defined daily dose; ECG, electrocardiogram; IQR, interquartile range; ms, millisecond; OPD, outpatient department; PDD, prescribed daily dose; QTc, corrected QT; WHO, World Health Organization.

Data Sharing Statement

We included all the relevant information, but further datasets can be obtained from the corresponding author if required.

Ethical Approval and Consent to Participate

First, ethical approval was obtained from the ethical review board in the School of Medicine and Health Science, University of Gondar (Ref No. SOM/1482/2022). Letter of cooperation was written to the selected hospitals from University of Gondar, College of Medicine and Health Science, Department of Human Physiology. Letter of permission was asked of the manager and department of internal medicine in all selected hospitals. The purpose of the study was explained to the study participants. They were assured confidentiality, as information obtained will not be disclosed to anyone, and written informed consent was done. Study participants were asked to sign the consent form to declare that the study was done based on their free decision. The study was conducted in compliance with the Declaration of Helsinki. Those study participants with ECG abnormality were linked to outpatient department of internal medicine for further inspection.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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