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RESEARCH ARTICLE

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH

Clinical characteristics of seizure recurrence and epilepsy development in patients with alcohol-related seizures

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Abstract

Background: Alcohol withdrawal is widely recognized as a trigger for acute symptomatic seizures among individuals with chronic alcohol consumption. While most alcohol withdrawal seizures occur shortly after cessation, chronic alcohol consumption can be associated with the development of epilepsy, necessitating anti-epileptic drug (AED) therapy. This study aimed to investigate the clinical characteristics, seizure recurrence, and epilepsy development in patients with alcohol-related seizures and to identify prognostic factors for epilepsy.

Methods: In a retrospective analysis at Ewha Womans University Mokdong Hospital, 206 patients with alcohol-related seizures were examined and 15 were excluded due to preexisting epilepsy. Demographic and clinical data, including alcohol withdrawal duration, seizure recurrence, types, and comorbidities, were investigated. Logistic regression models were used to analyze the risk factors for seizure recurrence and epilepsy development. The performance of the final models was evaluated based on the area under the receiver operating characteristic curve (AUC) and validated using calibration plots and leave-one-out cross-validation.

Results: Of the 191 patients (146 males; mean age 48.3 ± 12.1 years) with alcohol-related seizures, 99 patients (51.8%) experienced seizure recurrence and 79 patients (41.4%) developed epilepsy. Factors associated with seizure recurrence included alcohol consumption levels, occurrence of focal impaired awareness seizure, anxiety, and headache. The number of recurrent seizures, semiology, status epilepticus, electroencephalogram findings, and brain imaging findings was associated with epilepsy development. The predictive models showed strong diagnostic performance, with AUCs of 0.833 for seizure recurrence and 0.939 for epilepsy development.

Conclusion: High alcohol consumption and specific clinical and diagnostic features are significant predictors of seizure recurrence and the development of epilepsy among patients with alcohol-related seizures. These findings underscore the importance of early identification and intervention to prevent seizure recurrence and

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the onset of epilepsy, emphasizing the importance of AED treatment in managing these conditions.

KEYWORDS
alcohol-related seizures, electroencephalogram, epilepsy, epileptogenesis, seizure recurrence

INTRODUCTION

Alcohol withdrawal is known to cause acute symptomatic seizures (Hughes, 2009; Rogawski, 2005). The incidence of seizures in individuals with alcohol use disorder is three times higher than that in the general population (Hillbom et al., 2003). Prolonged alcohol consumption can inhibit nerve excitability by modifying the functional activity of gamma-aminobutyric acid (GABA) receptors (Rogawski, 2005; Wei et al., 2004). Sudden alcohol withdrawal results in drastic changes in cellular events at neurotransmitter receptors that lower the seizure threshold, thus leading to seizure events (Davis & Wu, 2001). Most alcohol withdrawal seizures occur within 48h of withdrawal (Hughes, 2009; Rathlev et al., 2006). The International League Against Epilepsy (ILAE) proposed a revised definition of epilepsy in 2014 that classifies alcohol-withdrawal seizures as acute symptomatic seizures and not epilepsy (Fisher et al., 2014; Scheffer et al., 2016).

However, according to the literature, chronic alcohol consumption might be related to epileptogenesis (Samokhvalov et al., 2010). Four theories have been proposed to support this hypothesis. First, long-term heavy alcohol users with alcohol-related seizures might have cerebral atrophy due to chronic alcohol intake (Kril & Halliday, 1999; Sullivan et al., 1996). Second, certain structural changes, including traumatic cerebral hemorrhage, might be more prevalent in heavy alcohol users (Rathlev et al., 2006). Third, the "kindling" theory demonstrates that repeated withdrawal gradually lowers the epileptogenic threshold (Ballenger & Post, 1978; Bartolomei, 2006; Becker, 1998). Fourth, seizures in heavy alcohol users can be explained by specific changes in neurotransmitter systems, including GABA, that cause hyperexcitability (Avoli, 1997; Bonthius et al., 2001; Olsen & Spigelman, 2012).

There is still controversy about whether alcohol withdrawal causes evoked seizures that do not require anti-epileptic drug (AED) or can induce epileptogenesis requiring an AED prescription (Hattemer et al., 2008). Several studies have reported alcohol-related seizure patients with focal seizure semiology or cortical lesions on brain imaging (Rathlev et al., 2006). Although such patients have a high probability of seizure recurrence and progression to epilepsy, treatment guidelines remain unclear.

In this study, we investigated the clinical characteristics, seizure recurrence, and epilepsy development of patients with alcohol-related seizures. In addition, we identified prognostic factors and developed a predictive model of epilepsy in these patients.

METHODS

Participants

We performed a retrospective review of the hospital records of patients who visited Ewha Womans University Mokdong Hospital for alcohol-related seizures from 2010 to 2022. Patients who were followed up at the hospital, through the outpatient clinic or emergency room, for more than 1 year after their first seizure episode were included; we excluded participants who had a history of pre-existing epilepsy. Additionally, we excluded patients previously diagnosed with stroke, head trauma, brain tumor, encephalitis, schizophrenia, or intellectual disability. Loss of consciousness events such as non-seizure episodes, syncope, and metabolic encephalopathy were not considered. Patients who quit drinking for more than a month prior to their first seizure were also excluded. Overall, we enrolled 191 patients who had a history of chronic alcohol consumption and acute seizures. Epilepsy was diagnosed based on the criteria of the ILAE (Fisher et al., 2017).

We investigated the following variables of patients with alcohol-related seizures in our study: the duration of alcohol withdrawal, the number of seizure recurrences, and the classification of seizure types as focal impaired awareness seizure (FIAS) or myoclonus. The patients were classified according to their semiology (a generalized group and a group with focal features such as lateralized head version, lateralized eyeball deviation, and partial seizure). Seizures occurring within 24h of the initial event were not considered as recurrences; only those with an inter-ictal period were classified as recurrences (Fisher et al., 2017). We examined whether the patients were diagnosed with epilepsy and prescribed AEDs and whether the patients presented with status epilepticus. Additionally, we collected information about the participants' underlying diseases, including a history of epilepsy, hypertension, diabetes mellitus, liver disease, and anxiety disorders, and we examined accompanying symptoms or signs such as headache, nausea, vomiting, and delirium tremens (DT).

This study was approved by the Ewha Womans University Hospital's Institutional Review Board. This was a retrospective and observational study; therefore, the requirement for informed consent was waived.

Alcohol consumption

Alcohol intake was quantified according to the standard criteria proposed by the National Institute on Alcohol Abuse and Alcoholism, which defines binge drinking as alcohol consumption that exceeds four standard drinks per day for males and three drinks per day for females (Gunzerath et al., 2004). In the case of beer, the level of consumption was determined based on those criteria. The quantity of traditional Korean alcohol was converted to standard drinks based on the alcoholic strength of traditional Korean drinks such as Korean rice beer (Makgeolli) and Korean liquor (Soju) (Lee et al., 2019).

Electroencephalogram findings and brain imaging findings

The participants underwent routine electroencephalogram (EEG) monitoring with 64 channels or continuous EEG monitoring with 19 channels following seizure events. We divided the participants into four groups based on their EEG findings: the normal EEG group; the group exhibiting background slow activity, excessive beta activity, or nonspecific findings; the group displaying continuous slow and background slow activity; and the group showing sharp waves.

Brain imaging was performed by either simple computed tomography or magnetic resonance imaging (MRI). In the case of MRI, diffusion-weighted, T1- and T2-weighted, fluid-attenuated inversion recovery, and gradient-echo images were obtained. Brain imaging findings were subdivided into four groups: the group with normal imaging findings, the group displaying diffuse cortical atrophy, the group showing subcortical lesions, and the group presenting with hippocampal atrophy.

Statistical analysis

The patients were divided into recurrence/non-recurrence groups and epilepsy/non-epilepsy groups. Demographic and clinical characteristics were compared between the groups using Student's *t*-test, the Kruskal–Wallis test for continuous variables, and the chi-square test for categorical variables. Logistic regression analyses were performed to examine the relationship between the occurrence of events (seizure recurrence and epilepsy development) and various risk factors. In multivariate analysis, the initial variable selection was performed based on univariate analysis with a p-value < 0.1 to identify potential risk factors. These factors were then used to fit the full model (multivariate model 1), from which backward elimination was applied to retain only significant variables for the final model (multivariate model 2). Feature selection was conducted independently within each leave-one-out cross-validation (LOOCV) fold to mitigate overfitting and ensure robustness. Evaluation of the final model was performed using receiver operating characteristic (ROC) curves, area under the ROC curve (AUC), sensitivity and specificity. Model calibration, which assesses the agreement between observed outcomes and predictions, was evaluated using calibration plots. Internal validation was performed using LOOCV to assess model stability and generalizability. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and the statistical significance level was set at 0.05.

RESULTS

Of the initial cohort of 269 patients with alcohol-related seizures, 78 individuals were excluded for meeting the exclusion criteria. Thus, 191 patients (146 males and 45 females) were included in the final analysis. The average age of all participants was 48.3 ± 12.1 years. The mean standard alcohol consumption per day was 9.4 ± 5.7 drinks. Among the participants, 99 (51.8%) experienced recurrent alcohol-related seizures, and 79 participants (41.4%) were diagnosed with epilepsy and prescribed AEDs.

A comparison of the clinical characteristics of participants with and without seizure recurrence, as well as those with and without epilepsy development, is presented in Table 1. As alcohol consumption increased, the proportion of seizure recurrence increased progressively ($p = 0.008$), but the proportion of epilepsy development did not show a specific trend (Figure 1). The presence of FIAS was associated with a higher recurrence rate ($p < 0.001$) and a greater likelihood of epilepsy diagnosis ($p < 0.001$). Additionally, the presence of focal features in semiology and MRI findings were associated with the development of epilepsy (semiology: $p < 0.001$; MRI findings: $p < 0.001$). EEG findings showed a significant correlation with seizure recurrence and epilepsy development (seizure recurrence, $p = 0.024$; epilepsy development, $p < 0.001$). Among comorbid conditions, the presence of anxiety disorders was associated with seizure recurrence ($p = 0.001$), and the presence of liver disease was linked to an epilepsy diagnosis ($p = 0.012$). Headache as an accompanying symptom was associated with both seizure recurrence and the development of epilepsy (seizure recurrence, $p < 0.001$; epilepsy development, $p = 0.002$). Nausea and vomiting were also associated with both seizure recurrence and the development of epilepsy (seizure recurrence, $p = 0.042$; epilepsy development, $p = 0.002$), and the presence of DT was associated with seizure recurrence ($p = 0.003$).

Table 2 shows the results of logistic regression analysis on risk factors for seizure recurrence. In univariate analyses, high alcohol consumption (>15 standard drinks/day, odds ratio (OR) 7.077, 95% confidence interval (CI) 2.275–25.519), the presence of focal seizure semiology (OR 6.655, 95% CI 2.431–23.461), diagnosis of epilepsy due to prescribed AEDs (OR 2.924, 95% CI 1.615–5.395), abnormal EEG and MRI findings (EEG: sharp wave, OR 2.847, 95% CI 1.364–6.109; MRI: subcortical lesions, OR 1.909, 95% CI 0.958–3.853; hippocampal atrophy, OR 2.436, 95% CI 0.953–6.547), comorbid anxiety disorder (OR 2.948, 95% CI 1.640–5.389), and the

TABLE 1 Clinical characteristics in patients with alcohol-related seizures.

	Total (N = 191)		No recurrence (N = 92)		Recurrence (N = 99)			No epilepsy (N = 112)		Epilepsy (N = 79)		
	N	%	N	%	N	%	p-value	N	%	N	%	p-value
Age							0.442					0.073
20–29	14	7.3	5	5.4	9	9.1		10	8.9	4	5.1	
30–39	30	15.7	14	15.2	16	16.2		20	17.9	10	12.7	
40–49	64	33.5	35	38.0	29	29.3		41	36.6	23	29.1	
50–59	53	27.7	27	29.3	26	26.3		30	26.8	23	29.1	
>=60	30	15.7	11	12.0	19	19.2		11	9.8	19	24.1	
Sex							0.912					0.832
Female	45	23.6	22	23.9	23	23.2		27	24.1	18	22.8	
Male	146	76.4	70	76.1	76	76.8		85	75.9	61	77.2	
Alcohol consumption amount group							0.008					0.473
1–5	36	18.8	23	25.0	13	13.1		17	15.2	19	24.1	
6–10	28	14.7	15	16.3	13	13.1		18	16.1	10	12.7	
11–15	102	53.4	49	53.3	53	53.5		62	55.4	40	50.6	
>15	25	13.1	5	5.4	20	20.2		15	13.4	10	12.7	
Alcohol withdrawal duration (h)							0.339					0.474
0–24	75	39.3	38	41.3	37	37.4		41	36.6	34	43.0	
24–48	46	24.1	25	27.2	21	21.2		26	23.2	20	25.3	
>=48	70	36.6	29	31.5	41	41.4		45	40.2	25	31.6	
Recurrence group												<0.001
0	92	48.2	92	100.0		0.0		66	58.9	26	32.9	
1–3	67	35.1		0.0	67	67.7		38	33.9	29	36.7	
>=4	32	16.8		0.0	32	32.3		8	7.1	24	30.4	
FIAS							<0.001					<0.001
No	164	85.9	88	95.7	76	76.8		108	96.4	56	70.9	
Yes	27	14.1	4	4.3	23	23.2		4	3.6	23	29.1	
Myoclonus							0.642					0.239
No	179	93.7	87	94.6	92	92.9		107	95.5	72	91.1	
Yes	12	6.3	5	5.4	7	7.1		5	4.5	7	8.9	
Semiology							0.582					<0.001
Generalized	144	75.4	71	77.2	73	73.7		100	89.3	44	55.7	
Focal features[a]	47	24.6	21	22.8	26	26.3		12	10.7	35	44.3	
AED prescription							<0.001					
No	112	58.6	66	71.7	46	46.5		112	100.0		0.0	
Yes	79	41.4	26	28.3	53	53.5			0.0	79	100.0	
Status epilepticus							0.263					<0.001
No	167	87.4	83	90.2	84	84.8		110	98.2	57	72.2	
Yes	24	12.6	9	9.8	15	15.2		2	1.8	22	27.8	
EEG group							0.024					<0.001
Normal	74	38.7	44	47.8	30	30.3		63	56.3	11	13.9	
BS, excessive beta, nonspecific	43	22.5	17	18.5	26	26.3		28	25.0	15	19.0	
CS and BS	11	5.8	4	4.3	7	7.1		4	3.6	7	8.9	

TABLE 1 (Continued)

	Total (N = 191)		No recurrence (N = 92)		Recurrence (N = 99)			No epilepsy (N = 112)		Epilepsy (N = 79)		
	N	%	N	%	N	%	p-value	N	%	N	%	p-value
SW	50	26.2	17	18.5	33	33.3		5	4.5	45	57.0	
Not available	13	6.8	10	10.9	3	3.0		12	10.7	1	1.3	
MRI group							0.164					<0.001
Normal	64	33.5	37	40.2	27	27.3		45	40.2	19	24.1	
Diffuse cortical atrophy	35	18.3	18	19.6	17	17.2		20	17.9	15	19.0	
Subcortical lesions	67	35.1	28	30.4	39	39.4		45	40.2	22	27.8	
Hippocampal atrophy	25	13.1	9	9.8	16	16.2		2	1.8	23	29.1	
Hypertension							0.769					0.287
No	143	74.9	68	73.9	75	75.8		87	77.7	56	70.9	
Yes	48	25.1	24	26.1	24	24.2		25	22.3	23	29.1	
Diabetes mellitus							0.052					0.681
No	167	87.4	76	82.6	91	91.9		97	86.6	70	88.6	
Yes	24	12.6	16	17.4	8	8.1		15	13.4	9	11.4	
Liver disease							0.518					0.012
No	54	28.3	24	26.1	30	30.3		24	21.4	30	38.0	
Yes	137	71.7	68	73.9	69	69.7		88	78.6	49	62.0	
Anxiety disorder							<0.001					0.292
No	105	55.0	63	68.5	42	42.4		58	51.8	47	59.5	
Yes	86	45.0	29	31.5	57	57.6		54	48.2	32	40.5	
Headache							<0.001					0.002
No	157	82.2	81	88.0	76	76.8		100	89.3	57	72.2	
Yes	34	17.8	11	12.0	23	23.2		12	10.7	22	27.8	
Nausea and vomiting							0.042					0.002
No	119	62.3	71	77.2	48	48.5		73	65.2	46	58.2	
Yes	72	37.7	21	22.8	51	51.5		39	34.8	33	41.8	
Delirium tremens							0.003					0.574
No	141	73.8	77	83.7	64	64.6		81	72.3	60	75.9	
Yes	50	26.2	15	16.3	35	35.4		31	27.7	19	24.1	

Abbreviations: *N*, number; AED, anti-epileptic drug; EEG, electroencephalogram; FIAS, focal impaired awareness seizure; MRI, magnetic resonance imaging; Ref., reference.

[a]Focal features: lateralizing signs such as head version and eyeball deviation.

presence of headache or DT as an accompanying symptom or sign (headache, OR 8.334, 95% CI 3.928–19.477; DTs, OR 2.807, 95% CI 1.431–5.726) were significantly associated with seizure recurrence. In constructing multivariate models by combining significant variables, we developed multivariate model 2 by incorporating only the significant variables in multivariate analysis. Multivariate model 2 contains the following predictors: (1) high alcohol consumption (>15 standard drinks/day; OR 6.580, 95% CI 1.571–27.563), (2) the presence of FIAS (OR 3.832, 95% CI 1.059–13.869), (3) diagnosis of epilepsy with AED prescription (OR 2.479, 95% CI 1.176–5.226), (4) comorbid anxiety disorders (OR 2.831, 95% CI 1.387–5.779), and (5) the presence of headache (OR 6.481, 95% CI 2.696–15.578) (Figure 2).

The predictive performance of the final multivariate model 2 was decent, with an AUC value of 0.820 (95% CI 0.778–0.888); the cross-validated AUC was 0.769 (95% CI 0.721–0.847) (Figure 3A).

Univariate and multivariate analyses to assess the association between risk factors and epilepsy development are shown in Table 3. Univariate analyses showed that older age (≥60 years, OR 4.317, 95% CI 1.150–18.959), alcohol withdrawal duration (24–48 h, OR 0.282, 95% CI 0.099–0.694), seizure recurrence rates (1–3 times, OR 1.937, 95% CI 1.001–3.782; ≥4 times, OR 7.615, 95% CI 3.147–20.156, compared with no recurrence), the presence of FIAS (OR 11.087, 95% CI 4.030–39.219), focal features in semiology (OR 6.629, 95% CI 3.224–14.454), presenting with status epilepticus (OR 21.227, 95% CI 5.969–135.416), abnormal EEG and MRI findings (EEG:

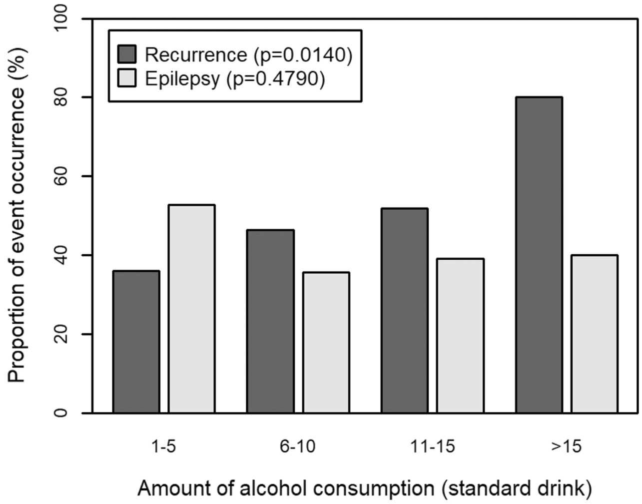

FIGURE 1 The proportion of alcohol-related seizure recurrence and epilepsy development according to the amount of alcohol consumed.

background slow (BS), excessive beta, nonspecific, OR 3.068, 95% CI 1.262–7.685; continuous slow and BS, OR 10.023, 95% CI 2.603–44.067; sharp wave, OR 51.545, 95% CI 18.147–176.869; MRI: hippocampal atrophy, OR 27.236, 95% CI 7.116–180.655), a history of liver disease (OR 0.445, 95% CI 0.233–0.842), and presence of concomitant symptoms or signs such as headache (OR 2.776, 95% CI 1.472–5.319), nausea and vomiting (OR 3.216, 95% CI 1.505–7.172) were significantly associated with the development of epilepsy. In the multivariate logistic regression model, (1) the seizure recurrence rate (≥4 times, OR 7.811, 95% CI 1.970–33.932), (2) focal features in semiology (OR 6.092, 95% CI 1.942–20.661), (3) presenting with status epilepticus (OR 13.155, 95% CI 2.399–119.221), (4) abnormal EEG findings (sharp wave, OR 26.960, 95% CI 8.422–102.348), and (5) abnormal MRI findings (hippocampal atrophy, OR 12.316, 95% CI 2.011–113.420) were significant, so these predictors were used to construct multivariate model 2 (Figure 2).

The final multivariate model 2 exhibited strong predictive performance, with an AUC value of 0.939 (95% CI 0.906–0.972), and the cross-validated AUC was at 0.910 (95% CI 0.865–0.952) (Figure 3B).

The calibration plot shown in Figure S1 revealed that the risk calibration curves were close to the diagonal, indicating that both models fit the data well.

DISCUSSION

In this study, we evaluated patients with at least one seizure who had a history of chronic alcohol consumption. We identified several risk factors associated with seizure recurrence: high alcohol consumption, presenting with FIAS, a diagnosis of epilepsy with AED prescription, history of epilepsy, the presence of comorbid anxiety disorder, and the experience of headache. Additionally, we found risk factors for the development of epilepsy: a high seizure recurrence rate, focal features in semiology, presenting with status epilepticus, and abnormal findings in EEG and MRI. The predictive models, which incorporate those predictors into multivariate logistic regression models for seizure recurrence and the development of epilepsy, demonstrated strong diagnostic performance.

The first major finding of our study is that high alcohol consumption, the presence of FIAS, a history of epilepsy, comorbid anxiety disorder, and concurrent symptoms of headache are risk factors for alcohol-related seizure recurrence. It is noteworthy that, despite the higher mortality rate of patients with alcohol-related seizures compared with the general population (Sansone et al., 2023), studies on these risk factors have been limited. Our findings are consistent with the previous study showing that age, sex, and time since the last drink were not significant predictors for seizure recurrence (D'Onofrio et al., 1999). However, the previous study did not address risk factors or build predictive models for seizure recurrence, including EEG and brain imaging. Animal studies have also shown that chronic alcohol consumption and repeated withdrawal can lead to spontaneous seizures, a persistent decrease in seizure threshold resembling "kindling" phenomenon (Kokka et al., 1993). Our study can assist in predicting seizure recurrence in patients with alcohol-related seizures and in developing strategies for recurrence prevention in clinical practice.

In our model for the development of epilepsy, the number of seizure events and semiology with focal features were risk factors, which is in agreement with the literature (Kim et al., 2016). According to the Status Epilepticus Severity Score, the significant predictors are age, history of seizures, seizure type, and extent of consciousness impairment (Rossetti et al., 2008). It has been proposed specific predictors for seizure recurrence and epilepsy in patients having their first seizure after ischemic stroke, such as male sex and partial seizure (Kim et al., 2016). In this study, an epileptiform discharge (sharp waves) on an EEG was an important predictor of epilepsy in patients with alcohol-related seizures. The univariate logistic regression model showed that epileptiform discharges had the highest OR of 55.659, suggesting that an epileptiform discharge might be the most effective predictor. Alcohol withdrawal seizures are generally known to be associated with a normal EEG (Sand et al., 2002). However, epileptiform discharges on an EEG can imply the presence of alcohol-independent epileptic factors or epileptogenesis caused by chronic alcohol consumption (Ballenger & Post, 1978; Bartolomei, 2006; Becker, 1998; Sullivan et al., 1996). Therefore, if a patient with alcohol use disorder experiences a seizure event and visits the hospital, the possibility of epilepsy must be considered if the EEG shows epileptiform discharges.

Hippocampal atrophy on brain MRI was significantly associated with the development of epilepsy. This result is in line with those of previous studies showing that alcohol-related seizure patients had more brain lesions (Bråthen et al., 1999; Rathlev et al., 2002; Verma et al., 1992). An earlier study with rats showed that exposing a developing brain to alcohol resulted in neuronal loss from the hippocampus (Bonthius et al., 2001). Additionally, adult rats subjected to chronic alcohol exposure showed significant cell loss in all hippocampal fields and reduced neural stem cell

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TABLE 2 Univariate and multivariate models for predicting seizure recurrences.

	Univariate analysis				Multivariate model 1				Multivariate model 2			
	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value
Age												
20–29	Ref.											
30–39	0.635	0.162	2.299	0.496								
40–49	0.460	0.129	1.485	0.205								
50–59	0.535	0.147	1.763	0.314								
>=60	0.960	0.243	3.550	0.951								
Sex												
Female	Ref.											
Male	0.963	0.492	1.886	0.912								
Alcohol consumption amount group												
1–5	Ref.				Ref.				Ref.			
6–10	1.533	0.560	4.248	0.406	1.547	0.421	5.678	0.511	1.541	0.440	5.402	0.499
11–15	1.914	0.885	4.279	0.104	2.030	0.702	5.873	0.191	2.353	0.861	6.434	0.095
>15	7.077	2.275	25.519	0.001	7.060	1.639	30.411	0.009	6.580	1.571	27.563	0.010
Alcohol withdrawal duration (h)												
0–24	Ref.											
24–48	1.253	0.573	2.762	0.572								
>=48	1.974	0.947	4.247	0.074								
Recurrence group												
0												
1–3												
>=4												
FIAS												
No	Ref.				Ref.				Ref.			
Yes	6.655	2.431	23.461	0.001	3.365	0.871	12.997	0.078	3.832	1.059	13.869	0.041
Myoclonus												
No	Ref.											
Yes	1.324	0.408	4.619	0.642								
Semiology												
Generalized	Ref.											
Focal features[a]	1.204	0.623	2.350	0.582								
AED prescription												
No	Ref.				Ref.				Ref.			
Yes	2.924	1.615	5.395	0.001	3.093	1.154	8.292	0.025	2.479	1.176	5.226	0.017
Status epilepticus												
No	Ref.											
Yes	1.647	0.693	4.117	0.267								
EEG group												
Normal	Ref.				Ref.							
BS, excessive beta, nonspecific	2.243	1.049	4.900	0.039	1.144	0.427	3.062	0.789				
CS and BS	2.567	0.711	10.523	0.160	0.585	0.103	3.314	0.544				
SW	2.847	1.364	6.109	0.006	0.811	0.251	2.625	0.727				

(Continues)

TABLE 2 (Continued)

	Univariate analysis				Multivariate model 1				Multivariate model 2			
	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value
Not available	0.440	0.093	1.579	0.241	0.300	0.052	1.728	0.178				
MRI group												
Normal	Ref.											
Diffuse cortical atrophy	1.294	0.564	2.976	0.542	0.571	0.187	1.748	0.327				
Subcortical lesions	1.909	0.958	3.853	0.068	1.464	0.620	3.457	0.385				
Hippocampal atrophy	2.436	0.953	6.547	0.068	0.564	0.137	2.318	0.427				
Hypertension												
No	Ref.											
Yes	0.907	0.470	1.748	0.769								
Diabetes mellitus												
No	Ref.											
Yes	0.418	0.162	1.003	0.058								
Liver disease												
No	Ref.											
Yes	0.812	0.429	1.526	0.518								
Anxiety disorder												
No	Ref.				Ref.				Ref.			
Yes	2.948	1.640	5.389	<0.001	2.584	1.170	5.706	0.019	2.831	1.387	5.779	0.004
Headache												
No	Ref.				Ref.				Ref.			
Yes	8.334	3.928	19.477	<0.001	6.896	2.698	17.623	<0.001	6.481	2.696	15.578	<0.001
Nausea and vomiting												
No	Ref.				Ref.							
Yes	2.228	1.038	5.042	0.045	1.601	0.580	4.423	0.364				
Delirium tremens												
No	Ref.				Ref.							
Yes	2.807	1.431	5.726	0.003	1.448	0.578	3.628	0.430				

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; AED, anti-epileptic drug; EEG, electroencephalogram; FIAS, focal impaired awareness seizure; MRI, magnetic resonance imaging; Ref., reference.

[a]Focal features: lateralizing signs such as head version and eyeball deviation.

proliferation, leading to decreased neurogenesis and suggesting functional and neuropathologic alterations associated with epilepsy (Ame et al., 1988; Scorza et al., 2003). Studies in humans have also demonstrated that chronic alcohol use can be associated with hippocampal atrophy (Lee et al., 2016; Topiwala et al., 2017). How hippocampal atrophy can contribute to the development of seizures in patients with alcohol use disorder is not completely understood, but disrupted neuronal networks in patients with alcohol-related hippocampal atrophy might lead to altered neuronal connections or changes in various neurotransmitter systems such as glutamate or GABA that contribute to an imbalance in neuronal excitability (Geibprasert et al., 2010). The development of epilepsy should be considered if a patient with a history of chronic alcohol use disorder and hippocampal atrophy on MRI manifests seizures.

In this study, semiology with focal features was significantly associated with an epilepsy diagnosis. This result is consistent with the existing literature showing that the semiological lateralizing sign could originate from the focal epileptogenic zone of the brain (Loddenkemper & Kotagal, 2005). Our findings demonstrate that more frequent seizure recurrence was also associated with a higher likelihood of receiving an epilepsy diagnosis. According to the "kindling" theory, even if alcohol withdrawal initially induces seizures, epileptic seizures can occur if those events accumulate because the epileptogenic threshold is lowered (Samokhvalov et al., 2010). Our study thus identified semiology with focal features and high

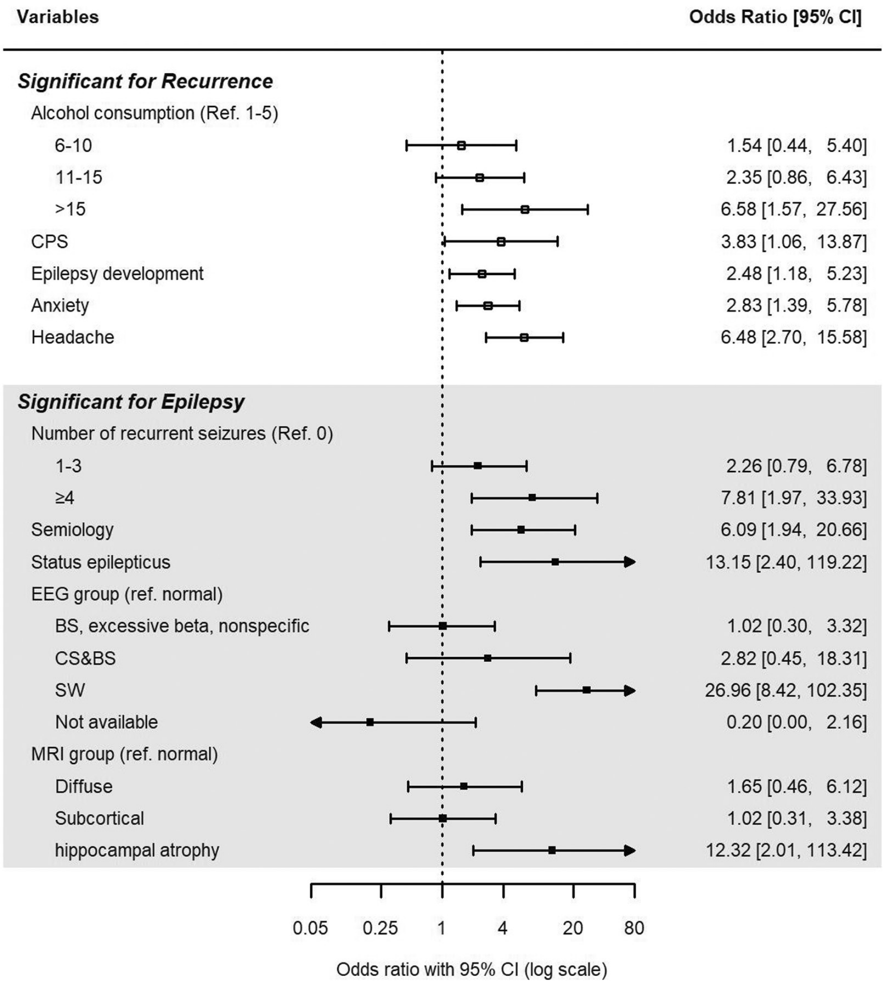

FIGURE 2 Forest plot showing odds ratios of significant risk factors predicting seizure recurrence (white region) and epilepsy development (shaded region).

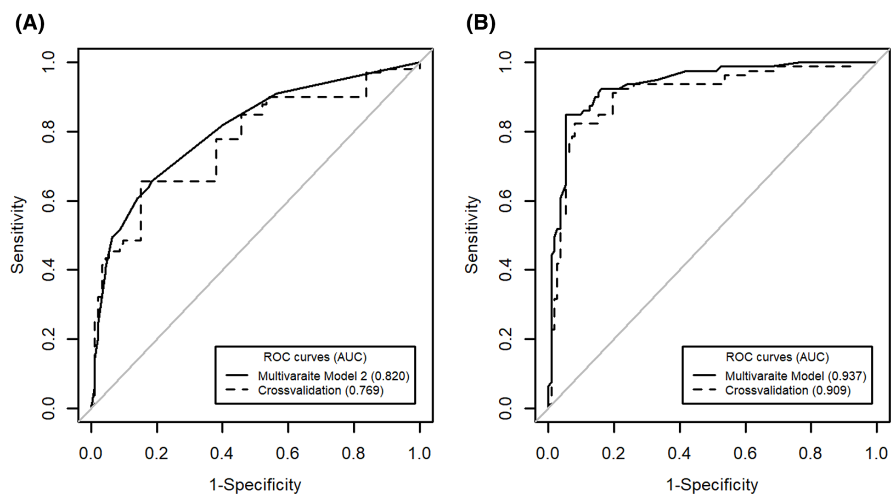

FIGURE 3 Receiver operating characteristic curves for the multivariate logistic regression model and leave-one-out cross-validated predictions for seizure recurrence (A) and epilepsy development (B).

recurrence frequency as important factors in the development of epilepsy.

The relationship between headaches, anxiety, and alcohol-related seizures might be explained by the impact of chronic alcohol use on the brain. Alcohol consumption is known to be associated with an increased risk of headaches, including tension-type headaches and migraines (Hindiyeh et al., 2020; Lebedeva et al., 2016; Wang et al., 2013). Comorbid headaches and epilepsy are also relatively

TABLE 3 Univariate and multivariate models to predict epilepsy development.

	Univariate analysis				Multivariate model 1				Multivariate model 2			
	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value
Age												
20–29	Ref.											
30–39	1.250	0.324	5.463	0.753	3.623	0.317	41.453	0.301				
40–49	1.402	0.416	5.570	0.601	6.188	0.620	61.817	0.121				
50–59	1.916	0.561	7.702	0.320	2.276	0.225	23.048	0.486				
>=60	4.317	1.150	18.959	0.037	12.002	1.035	139.198	0.047				
Sex												
Female	Ref.											
Male	0.929	0.465	1.826	0.833								
Alcohol consumption amount group												
1–5	Ref.											
6–10	0.497	0.176	1.352	0.176								
11–15	0.577	0.266	1.241	0.160								
>15	0.596	0.208	1.664	0.327								
Alcohol withdrawal duration (h)												
0–24	Ref.				Ref.							
24–48	0.282	0.099	0.694	0.010	1.012	0.262	3.908	0.987				
>=48	1.161	0.561	2.401	0.686	1.035	0.258	4.150	0.961				
Recurrence group												
0	Ref.				Ref.				Ref.			
1–3	1.937	1.001	3.782	0.051	1.839	0.519	6.513	0.345	2.256	0.787	6.779	0.134
>=4	7.615	3.147	20.156	<0.001	10.723	2.161	53.198	0.004	7.811	1.970	33.932	0.004
FIAS												
No	Ref.				Ref.							
Yes	11.087	4.030	39.219	<0.001	3.687	0.553	24.569	0.178				
Myoclonus												
No	Ref.											
Yes	2.081	0.640	7.269	0.226								
Semiology												
Generalized	Ref.				Ref.				Ref.			
Focal features[a]	6.629	3.224	14.454	<0.001	5.610	1.486	21.180	0.011	6.092	1.942	20.661	0.003
AED prescription												
No												
Yes												
Status epilepticus												
No	Ref.				Ref.				Ref.			
Yes	21.227	5.969	135.416	<0.001	19.225	2.600	142.170	0.004	13.155	2.399	119.221	0.008
EEG group												
Normal	Ref.				Ref.				Ref.			
BS, excessive beta, nonspecific	3.068	1.262	7.685	0.014	0.615	0.159	2.372	0.480	1.018	0.296	3.321	0.977
CS and BS	10.023	2.603	44.067	0.001	1.726	0.231	12.924	0.595	2.821	0.446	18.313	0.266
SW	51.545	18.147	176.869	<0.001	20.655	5.270	80.947	<0.001	26.960	8.422	102.348	<0.001
Not available	0.477	0.025	2.823	0.498	0.132	0.005	3.357	0.220	0.195	0.005	2.158	0.274

TABLE 3 (Continued)

	Univariate analysis				Multivariate model 1				Multivariate model 2			
	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value
MRI group												
Normal	Ref.				Ref.				Ref.			
Diffuse cortical atrophy	1.776	0.751	4.210	0.189	1.387	0.353	5.444	0.639	1.653	0.455	6.125	0.445
Subcortical lesions	1.158	0.553	2.442	0.698	0.897	0.231	3.474	0.875	1.020	0.308	3.385	0.974
Hippocampal atrophy	27.236	7.116	180.655	<0.001	10.628	1.448	78.032	0.020	12.316	2.011	113.420	0.012
History of epilepsy												
No	Ref.											
Yes	1.429	0.738	2.766	0.288								
Hypertension												
No	Ref.											
Yes	0.831	0.332	1.978	0.682								
Diabetes mellitus												
No	Ref.				Ref.							
Yes	0.445	0.233	0.842	0.013	0.735	0.208	2.595	0.633				
Liver disease												
No	Ref.											
Yes	0.731	0.407	1.306	0.292								
Anxiety disorder												
No	Ref.				Ref.							
Yes	2.776	1.472	5.319	0.002	0.889	0.253	3.127	0.854				
Headache												
No	Ref.				Ref.							
Yes	3.216	1.505	7.172	0.003	3.147	0.838	11.821	0.090				
Nausea and vomiting												
No	Ref.											
Yes	0.827	0.422	1.593	0.575								
Delirium tremens	1.250	0.324	5.463	0.753	3.623	0.317	41.453	0.301				
No	1.402	0.416	5.570	0.601	6.188	0.620	61.817	0.121				
Yes	1.916	0.561	7.702	0.320	2.276	0.225	23.048	0.486				

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; AED, anti-epileptic drug; EEG, electroencephalogram; FIAS, focal impaired awareness seizure; MRI, magnetic resonance imaging; Ref., reference.

[a]Focal features: lateralizing signs such as head version and eyeball deviation.

common, as both migraine and epilepsy share multiple common triggers such as sleep deprivation, female hormone fluctuations, visual stimulation, and alcohol (Kingston & Schwedt, 2017). Additionally, anxiety is significantly more prevalent in patients with alcohol use disorder (AUD), particularly during alcohol withdrawal syndrome. Repeated alcohol withdrawal increases anxiety in rats through mechanisms involving GABAA, corticotropin-releasing factor (CRF)1, and 5-HT3 receptors, implicating the limbic system, especially the amygdala (Faingold et al., 2004). Since seizures adversely affect patients' physical and emotional well-being, many patients experience depression or anxiety immediately following a seizure (Gutmane et al., 2019). Therefore, the co-occurrence of headaches and anxiety in patients with alcohol-related seizures can be attributed to both the direct effects of alcohol on brain physiology and shared risk factors for these conditions. Understanding this temporal relationship could support the "kindling" hypothesis and the concept of worsening emotional distress (hyperkatifeia) with repeated cycles of addiction, as proposed by George Koob (Koob & Schulkin, 2019). Further studies considering these aspects may elucidate the complex interplay between anxiety, AUD, and seizure risk.

The high sensitivity of these models offers valuable potential for the early prediction of seizure recurrence and the development of epilepsy, allowing for timely prescriptions of AEDs when patients with alcohol use disorder present with seizures at the hospital. There has been a lack of proposed models for predicting seizure recurrence or the progression to epilepsy in these patients (Manthey et al., 2019), despite the increasing prevalence of alcohol-related seizures in clinical practice (Hughes, 2009). Our models could contribute to the diagnosis and proper treatment of these patients in clinical settings.

Although we could not perform a prospective analysis in this study, we observed that the diagnoses of 20 patients (9.7%) changed during follow-up. They were initially diagnosed with alcohol withdrawal seizures and discharged without an AED prescription because they had no abnormalities on their EEG or brain imaging and no focal features. However, they continued to visit the hospital with recurrent seizures regardless of the alcohol withdrawal duration. They also started to show abnormal findings on the follow-up EEG and brain imaging, and AEDs were finally prescribed with an epilepsy diagnosis. If a cohort analysis can be performed, the characteristics of these patients might be further defined. Nevertheless, an advantage of this study is that a large number of participants ($n = 191$) underwent brain CT or MRI, and 181 participants (94.8%) underwent EEG monitoring.

This study has several limitations. First, although we examined daily alcohol consumption, we could not assess the overall alcohol consumption during the patient's lifetime or the total amount of alcohol consumed. Second, serum ethanol levels were not documented. Additionally, the degree of diffuse cortical atrophy was not quantified. Future studies could explore the relationship between the severity of atrophy and the development of epilepsy in patients with alcohol-related seizures. Third, although we excluded participants with a documented history of significant head injury to focus on patients with alcohol use disorder without obvious structural brain abnormalities, undiagnosed or subclinical head trauma may have occurred in our participants, potentially influencing our results. Fourth, generalizations from this study should be made with caution because it was conducted in a single hospital. Finally, this study was retrospective, which lacks prospective control. Future prospective studies are needed to validate our findings and improve the robustness of the predictive models.

CONCLUSION

Alcohol-related seizure patients exhibiting focal features, a history of recurrent seizure, epileptiform discharges, and brain cortical lesions are at high risk of being diagnosed with epilepsy. This study has demonstrated that alcohol can not only induce provoked recurrent seizures but also predispose to epilepsy, which needs to be treated with AEDs. Alcohol consumption and recurrent seizures can lead to epileptogenesis in the brains of patients with alcohol-related seizures.

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CONFLICT OF INTEREST STATEMENT

All authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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