Section: Neurology

Original Research Article

ALCOHOL-USE SEVERITY AND SEIZURE CLUSTERING IN ALCOHOL-RELATED SEIZURES: A SECONDARY ANALYSIS OF A PREVIOUSLY REPORTED TERTIARY-CARE COHORT

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Received : 03/09/2026
Received in revised form : 01/10/2026
Accepted : 13/10/2026

Keywords:
Alcohol-related seizures; seizure clustering; alcohol withdrawal; AUDIT; alcohol use disorder.

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DOI: 10.47009/jamp.2026.8.5.185

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2026; 8 (5); 1164-1167

ABSTRACT

Background: Alcohol-related seizures commonly occur in the setting of chronic alcohol exposure and withdrawal. The relationship between severity of alcohol use and seizure clustering is incompletely characterized. **Objective:** To examine the association between Alcohol Use Disorders Identification Test (AUDIT) score and seizure clustering and identify factors independently associated with clustering. **Materials and Methods:** Secondary analysis of 100 patients from a previously reported south Indian tertiary-care center cohort recruited from December 2019 to December 2020. Clustering was defined as ≥3 seizures within 24 hours with recovery between seizures. AUDIT was analyzed continuously and as <20 versus ≥20. Univariable comparisons and multivariable logistic regression were performed. **Results:** All 100 patients were male. Mean age was 53.17±12.72 years and mean AUDIT score was 21.72±5.05; 71% had AUDIT ≥20. Clustering occurred in 45%. Mean AUDIT was higher with clustering than without (23.36±3.48 vs 20.38±5.74; P=.002). AUDIT ≥20 was associated with clustering (OR 8.54; P<.001). In the primary multivariable model, AUDIT remained associated with clustering (adjusted OR 1.13 per point, 95% CI 1.02–1.25; P=.019), as did withdrawal symptoms (adjusted OR 5.15; 95% CI 1.15–22.95; P=.032) and previous withdrawal seizures (adjusted OR 12.55; 95% CI 2.15–73.40; P=.005). **Conclusion:** Higher AUDIT scores were associated with seizure clustering. The findings support standardized assessment of alcohol-use severity as an adjunct to clinical assessment, while causal inference is limited by the observational design.

INTRODUCTION

Alcohol consumption is an important modifiable risk factor associated with seizures and epilepsy. Epidemiological evidence has demonstrated an association between heavy alcohol consumption and seizures, while alcohol withdrawal may further lower seizure threshold through neuroadaptive changes associated with chronic exposure and abrupt reduction or cessation of intake.[1,2]

Repeated withdrawal episodes have been proposed to contribute to progressively increased neuronal excitability, forming the basis of the alcohol-withdrawal kindling hypothesis.[3,4] The clinical severity of alcohol use, however, is not necessarily captured by the volume consumed during a single drinking episode. The Alcohol Use Disorders Identification Test (AUDIT) was developed as a standardized measure of hazardous and harmful alcohol use and incorporates multiple dimensions of alcohol-related behavior.[5]

The original study from which the present dataset was derived examined clinical characteristics and seizure clustering among patients with alcohol-related seizures.[6] The present study is a secondary analysis of the same previously reported cohort, focusing specifically on the relationship between AUDIT-defined alcohol-use severity and seizure clustering.

Objective

To determine whether AUDIT score is associated with seizure clustering among patients presenting with alcohol-related seizures and to identify clinical factors independently associated with clustering.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

MATERIALS AND METHODS

Study design and setting

This was a secondary observational analysis of a previously reported cohort from the Department of Neurology, Thanjavur Medical College, Tamil Nadu, India by the same authors. The original cohort was recruited between December 2019 and December 2020. The present analysis used the existing dataset and included all 100 unique records. Reporting was structured according to STROBE recommendations.[7]

Participants

The original study enrolled consecutive patients presenting with alcohol-related seizures after application of its eligibility criteria. Patients with known epilepsy or another proximate cause of seizures were excluded in the original study.[6] No new participants were recruited for the present analysis.

Outcome and exposure definitions

The primary outcome was seizure clustering, defined as three or more seizures within 24 hours with complete recovery between seizures.[6] The principal exposure was AUDIT score, analyzed continuously and categorically using <20 versus ≥20.

Available alcohol-use variables included duration of alcohol consumption, beverage type, frequency of consumption, daily beverage volume, last-bout volume, recent change in drinking pattern, time from last bout to seizure, previous delirium tremens, withdrawal symptoms, and previous withdrawal seizures.

Beverage quantity was retained as milliliters of beverage. Because the dataset did not provide sufficient information to standardize beverage concentrations, volume was not converted to grams of ethanol.

Seizure and investigation variables

Seizure semiology, CT findings, MRI findings, and EEG findings were analyzed according to the categories present in the original dataset.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, and categorical variables as frequencies and percentages. Student t test was used for continuous variables and chi-square or Fisher exact test for categorical variables, as appropriate. The association between AUDIT category and clustering was examined using Fisher exact testing and an odds ratio. Multivariable logistic regression was performed with clustering as the dependent variable and AUDIT score, age, duration of alcohol use, withdrawal symptoms, and previous withdrawal seizures as predictors. Two-sided P<.05 was considered statistically significant.

Ethics

The original study was undertaken after IEC approval and written informed consent.

RESULTS

All 100 participants were male. Mean age was 53.17±12.72 years (range 30–87), and mean duration of alcohol use was 19.95±10.17 years. Mean AUDIT score was 21.72±5.05 (range 10–40), with 71% having AUDIT ≥20. Brandy was the most commonly reported beverage (67%), and 87% reported daily consumption. Withdrawal symptoms were recorded in 79% and previous withdrawal seizures in 14%.

Seizure clustering occurred in 45%. Generalized tonic-clonic seizures were present in 91%, focal to bilateral tonic clonic seizures in 8%, and focal seizures in 1%. CT was normal in 78% and showed generalized atrophy in 22%; MRI was normal in 95%.

Patients with clustering were older (57.07±12.50 vs 49.98±12.10 years; P=.005), had longer alcohol exposure (23.58±10.00 vs 16.98±9.39 years; P=.001), and had higher AUDIT scores (23.36±3.48 vs 20.38±5.74; P=.002). Daily beverage volume and last-bout volume were not significantly different between groups.

AUDIT ≥20 was present in 41/45 patients with clustering and 30/55 without clustering, corresponding to an OR of 8.54 (P<.001).

In multivariable analysis, AUDIT score remained independently associated with clustering (adjusted OR 1.130; 95% CI 1.020–1.251; P=.019). Withdrawal symptoms (adjusted OR 5.147; 95% CI 1.154–22.951; P=.032) and previous withdrawal seizures (adjusted OR 12.548; 95% CI 2.145–73.400; P=.005) were also independently associated. Age and duration of alcohol use were not independently associated after adjustment.

Table 1: Principal comparison according to seizure clustering

Variable	No clustering (n=55)	Clustering (n=45)	P value
Age, years	49.98±12.10	57.07±12.50	.005
Duration of alcohol use, years	16.98±9.39	23.58±10.00	.001
Daily beverage volume, mL	293.73±233.54	306.67±242.87	.788
Last-bout beverage volume, mL	464.73±194.39	495.33±197.28	.439
AUDIT score	20.38±5.74	23.36±3.48	.002

Table 2: Multivariable logistic regression for seizure clustering

Predictor	Adjusted OR	95% CI	P value
AUDIT score, per 1-point increase	1.130	1.020–1.251	.019
Age, per year	1.023	0.970–1.078	.402
Duration of alcohol use, per year	1.052	0.984–1.126	.138
Withdrawal symptoms	5.147	1.154–22.951	.032
Previous withdrawal seizures	12.548	2.145–73.400	.005

ISSN (O): 2687-5365; ISSN (P): 2753-6556

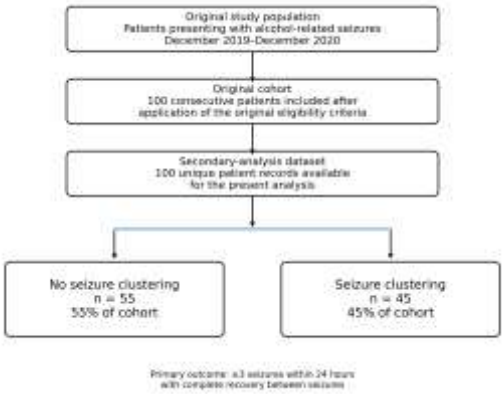


Figure 1: Participant flow and analytic groups

DISCUSSION

Although the previous study assessed alcohol-use severity using the AUDIT, the independent association between AUDIT score and seizure clustering was not specifically examined after accounting for other withdrawal-related factors. Therefore, the present secondary analysis evaluated this association using multivariable logistic regression. The principal finding of this secondary analysis was that higher AUDIT scores were associated with seizure clustering. The association remained after adjustment for age, duration of alcohol use, withdrawal symptoms, and previous withdrawal seizures. This finding is clinically relevant because AUDIT captures several dimensions of alcohol-use severity rather than beverage volume alone. Gutmane et al. similarly found high AUDIT scores to be common among patients presenting with alcohol-related seizures, supporting the use of standardized alcohol-use assessment in this population.[9]

Beverage volume was not associated with clustering in our cohort. However, beverage volume was recorded in millilitres rather than as grams of ethanol, and the alcohol concentration varied by beverage type. Therefore, the absence of an association should be interpreted cautiously. The present dataset recorded beverage volume rather than standardized grams of ethanol, and beverage concentrations varied by beverage type. The contrast between AUDIT score and beverage volume in our analysis therefore suggests that a multidimensional measure of alcohol-use severity may capture clinically relevant exposure characteristics that are not represented by volume alone. This interpretation is consistent with the findings of Gutmane et al., although their study compared patients with alcohol-related seizures with patients with alcohol dependence without seizures and did not specifically evaluate seizure clustering.[9]

Previous withdrawal seizures were strongly associated with clustering in our cohort. This observation is biologically plausible in light of the proposed neuroadaptation associated with repeated alcohol withdrawal. The kindling hypothesis has received support from clinical studies, including evidence that repeated detoxification or withdrawal episodes are associated with subsequent withdrawal seizures, although the relationship is not uniform across all studies.[3,4,12] More recent work has also emphasized that the kindling model should be regarded as one possible mechanism rather than a complete explanation of seizure recurrence.[12,13] Kádár et al., in a large retrospective study of alcohol-withdrawal admissions, found that a history of alcohol-related seizures and delirium tremens were associated with subsequent alcohol-related seizures, while their prospective component did not demonstrate that the presence of seizures necessarily increased the overall severity of withdrawal.[13]

These findings provide a useful context for our observation that previous withdrawal seizures were independently associated with clustering.

The seizure phenotype in our cohort was predominantly generalized tonic-clonic, with focal-to-bilateral tonic-clonic seizures in 8% and focal seizures in 1%. Sand et al. reported that alcohol-related seizures are usually generalized, and found that clearly abnormal EEG findings were more suggestive of epilepsy or another symptomatic seizure etiology, whereas a normal EEG had limited positive predictive value for alcohol-related seizures.[10] The recent study by Chun et al. is particularly relevant to the longer-term significance of seizure phenotype: among 191 patients with alcohol-related seizures, seizure recurrence was associated with higher alcohol consumption and focal impaired-awareness seizures, while recurrent seizures, seizure semiology, EEG and brain-imaging findings were associated with subsequent epilepsy development.[15] Our study was not designed to assess long-term epilepsy development, but these observations support careful characterization of focal features when evaluating patients with alcohol-related seizures.

The 45% clustering rate in our cohort should be interpreted in relation to the operational definition used. Haut's review highlighted substantial heterogeneity in definitions of seizure clustering, with commonly used clinical definitions including three seizures within 24 hours, but emphasized that no single universal clinical definition exists.[11]

Our prespecified definition of three or more seizures within 24 hours with recovery between events was retained from the original cohort to preserve consistency. Accordingly, the present findings should not be interpreted as a prevalence estimate directly comparable with studies using different cluster definitions or populations.

The findings also need to be considered against evidence on longer-term recurrence. Sansone et al. followed 199 patients after alcohol-withdrawal seizures and found delayed relapse in 11%, with previous alcohol-withdrawal seizures, skull fracture and possibly epileptiform EEG abnormalities associated with relapse.[14] Chun et al. reported substantially higher recurrence in a broader alcohol-

ISSN (O): 2687-5365; ISSN (P): 2753-6556

related seizure cohort, with 51.8% experiencing recurrence and 41.4% developing epilepsy during follow-up.[15] The apparent difference from our 45% clustering frequency is expected because clustering represents repeated seizures within the acute presentation period, whereas these studies evaluated recurrence over substantially longer follow-up periods and used different outcome definitions. Together, these studies reinforce the importance of distinguishing acute seizure clustering from delayed seizure recurrence and epilepsy development.

CONCLUSION

The study therefore adds a specific observation to the existing literature: within this South Indian tertiary-care cohort, AUDIT-defined alcohol-use severity was independently associated with acute seizure clustering after adjustment for clinically relevant withdrawal variables. The available comparator literature has largely addressed alcohol exposure, withdrawal severity, EEG findings, or subsequent seizure recurrence rather than directly testing the relationship between AUDIT score and acute seizure clustering.[9–15] Prospective multicenter studies using standardized ethanol exposure in grams, validated withdrawal scales, systematic EEG assessment, and longitudinal follow-up are warranted to determine whether AUDIT provides incremental predictive value beyond established withdrawal-related risk factors.

Higher AUDIT scores were associated with seizure clustering in this cohort of patients with alcohol-related seizures. Withdrawal symptoms and previous withdrawal seizures were also independently associated with clustering. Prospective multicenter studies using standardized ethanol exposure measurements and systematic assessment of metabolic and withdrawal-related confounders are warranted.

Author contributions: M.T. contributed to conception, original data collection, interpretation and manuscript development; E.M.J. contributed to analysis, interpretation and manuscript preparation; L.S.P. contributed to clinical data collection, interpretation and critical revision. All authors approved the final manuscript.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556