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CORRELATION OF ALCOHOLIC SEVERITY HEPATIC IMPAIRMENT AND DELIRIUM TREMENS

General Medicine

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ABSTRACT

Background: The study investigated the correlation between chronic alcohol use, hepatic impairment, and the incidence of delirium tremens in hospitalized patients. **Methods:** A retrospective cohort study was conducted with a sample size of 200 subjects from HIMS Teaching Hospital, Hassan. Data collected included demographic details, AUDIT scores, CIWA-Ar scores, and hepatic impairment types. **Results:** Of the 200 study participants, 45 (22.5%) presented with delirium tremens. Those with delirium tremens had an average age of 47.5 ± 10.9 years and a significantly higher mean AUDIT score of 25.2 ± 4.1 ($p<0.001$). The CIWA-Ar score for withdrawal severity was also higher at 18.3 ± 4.5 ($p<0.001$). Alcoholic hepatitis was prevalent in 55.6% of those with delirium, contrasting with 29% in those without ($p=0.012$). Cirrhosis was less common in those with delirium tremens (11.1%) as opposed to 38.7% in those without ($p=0.003$). **Conclusion:** The study emphasizes the relationships between alcohol use, hepatic impairment, and the manifestation of delirium tremens. Tools like AUDIT and CIWA- Ar are crucial for early recognition and management, potentially improving patient outcomes.

KEYWORDS

Chronic alcohol use, Hepatic impairment, Delirium tremens, AUDIT, CIWA-Ar, Hospitalized patients.

INTRODUCTION

Alcohol use disorder (AUD) represents a significant global health concern. It is the third leading preventable cause of death in the United States and contributes to a broad range of health and social issues worldwide [1]. Chronic alcohol consumption can lead to various physiological and psychological consequences, among which hepatic impairment and delirium tremens (DT) are particularly severe manifestations. This introduction reviews the interplay between alcoholic severity, hepatic dysfunction, and the onset of DT, with an emphasis on their intricate relationship.

Alcohol has been consumed by humans for millennia for its psychotropic effects and social implications. While moderate alcohol consumption might have potential health benefits for certain individuals, excessive and prolonged intake is detrimental [2]. AUD, characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences, has a global prevalence that remains alarmingly high [3]. The physiological and psychological repercussions of AUD are manifold, but the association with liver disease and neurological complications such as DT are of paramount concern.

The liver, as the primary site of alcohol metabolism, is especially vulnerable to the toxic effects of excessive alcohol intake. Chronic alcohol consumption leads to a spectrum of liver diseases – from fatty liver (steatosis) to alcoholic hepatitis, fibrosis, cirrhosis, and even hepatocellular carcinoma [4]. Alcoholic liver disease (ALD) represents a significant morbidity and mortality risk for individuals with AUD, with the severity of liver damage often correlating with the extent and duration of alcohol intake [5]. The interplay between alcohol metabolism and liver injury involves oxidative stress, mitochondrial dysfunction, and inflammation, leading to hepatocyte injury and death [6]. Importantly, hepatic impairment can exacerbate the neurotoxic effects of alcohol, providing a potential link between liver damage and DT.

DT represents the most severe form of alcohol withdrawal syndrome (AWS). Manifested by a rapid onset of confusion, tremors, hyperactivity, and hallucinations, it can also be accompanied by significant cardiovascular instability and has a substantial risk of mortality if not promptly and adequately treated [7]. The exact pathophysiology of DT remains incompletely understood, but it is believed to be due to an acute imbalance in neurotransmitter systems, particularly GABAergic and glutamatergic signaling, following abrupt cessation or reduction in alcohol intake in dependent individuals [8].

There is growing evidence suggesting a link between the severity of hepatic impairment and the risk of developing DT. Patients with significant liver damage appear to have a heightened risk for severe AWS and DT [9]. The liver's role in metabolizing and detoxifying various substances, including alcohol, could potentially modulate the central nervous system's response to alcohol withdrawal.

The multifactorial nature of DT onset implies a complex relationship with alcoholic severity and hepatic impairment. Individuals with severe AUD who have consumed high quantities of alcohol for extended periods tend to have greater hepatic damage [10]. This hepatic impairment might increase the risk of developing DT due to a reduced ability of the liver to detoxify and metabolize alcohol and its by-products, exacerbating the neurotoxic effects of alcohol withdrawal [11].

Furthermore, chronic alcohol consumption might also potentiate hepatic encephalopathy in those with advanced liver disease, further complicating the clinical presentation and potentially acting synergistically with DT [12]. Given this intricate relationship, a comprehensive understanding of the interplay between AUD severity, hepatic damage, and DT is essential for effective prevention, early diagnosis, and treatment.

In summary, AUD remains a significant global health issue with far-reaching consequences. The intricate association between alcoholic severity, hepatic impairment, and DT underscores the need for further research to unravel these connections, thereby facilitating better clinical outcomes for affected individuals.

Objectives

1. To determine the correlation between alcoholic severity and hepatic impairment.
2. To assess the relationship between hepatic impairment and the risk of delirium tremens.
3. To understand potential predictors of delirium tremens among chronic alcohol users.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective cohort study conducted at the Department of

General Medicine at HIMS Teaching Hospital, Hassan.

Study Duration
The study spanned a period of six months, from April 2022 to September 2023.

Source Of Data
Data were collected from all inpatients who presented to the department and met the established inclusion criteria.

Sample Size
In 15% of all patients without delirium tremens there were no signs of liver disease on admission in a multinational study spearheaded by Bode JC and associates.

The sample size (n) is calculated according to the formula: $n = z^2 * p * (1 - p) / e^2$
Where: z = 1.96 for a confidence level (α) of 95%, p = proportion (expressed as a decimal), e = margin of error.
- z = 1.96, p = 0.15, e = 0.05
- n = 1.962 * 0.15 * (1 - 0.15) / 0.052
- n = 0.4898 / 0.0025 = 195.922
- n ≈ 196

The sample size is equal to 196

For practical considerations, the study enrolled a rounded number of 200 subjects.

Inclusion Criteria
- Adults aged 18 years and above.
- Confirmed history of alcohol use.
- Those admitted with a diagnosis of hepatic impairment or delirium tremens.

Exclusion Criteria
- Patients diagnosed with liver diseases not related to alcohol.
- Patients with delirium resulting from causes other than alcohol withdrawal.

Methodology
Patient Identification:
- **Database Utilization:** Hospital databases were leveraged to pinpoint potential participants based on their medical histories.
- **Screening:** Records were initially analyzed to determine patient eligibility for the study.

Data Collection:
- **Primary Data:** Interviews or surveys were conducted with patients to obtain firsthand details about their patterns of alcohol consumption and the subsequent impact on their liver health.
- **Secondary Data:** Medical records were accessed to gather data on hepatic health evaluations, interventions employed, and the outcomes observed.
- **Data Recording:** A standardized form was employed to ensure systematic recording of all collected data.

Clinical Assessments:
- **Diagnostic Criteria:** Clear criteria were set for diagnosing hepatic impairment and delirium tremens. This often involved a combination of laboratory tests and clinical evaluations.
- **Severity Assessment:** Established scales were utilized to gauge the severity of both alcohol usage and the extent of hepatic damage. Notably, the AUDIT scale was used to assess alcohol severity, and the CIWA-Ar scale was employed to evaluate the severity of alcohol withdrawal symptoms.

Statistical Analysis
During the data preparation phase, the gathered data were first imported into the SPSS v26 software for a comprehensive analysis. An initial step involved addressing any missing data points to uphold the dataset's integrity. Additionally, any potential inconsistencies present within the dataset were meticulously identified and rectified before initiating any formal analysis. Following this, the study delved into descriptive statistics. For the continuous data, measures of central tendency such as the mean and median were computed, along with measures of dispersion, notably the standard deviation and range. In contrast, for the categorical data, frequency distributions were generated to gain a better understanding of the data distribution. For the inferential statistics, to discern the relationships between various variables, suitable statistical tests were selected. The chi-square test was employed for categorical data. Meanwhile, for continuous data, based on the data's nature and distribution, either the t-test or ANOVA was chosen and applied.

RESULTS
This study aimed to investigate the incidence of delirium tremens in chronic alcohol users and to identify potential predictors and correlates of this severe withdrawal symptom. The relationships between alcohol use severity, as quantified by the AUDIT score, withdrawal severity indicated by the CIWA-Ar score, and hepatic impairment with the occurrence of delirium tremens were particularly examined.

Table 1: Incidence of Delirium Tremens Among Study Participants

Status	Number (%)
With Delirium Tremens	45 (22.5%)
Without Delirium Tremens	155 (77.5%)

In our cohort of 200 study participants, 45 individuals (22.5%) presented with delirium tremens, while the majority, 155 participants (77.5%), did not manifest this severe withdrawal symptom (Table 1).

Table 2: Demographic and Baseline Clinical Characteristics of Participants

Parameter	Total (200)	With Delirium (45)	Without Delirium (155)	p-value
Age (Mean ± SD)	45.2 ± 12.3 years	47.5 ± 10.9	44.3 ± 12.8	0.033
Gender (n, %)	Male: 130 (65%), Female: 70 (35%)	Male: 30 (66.7%), Female: 15 (33.3%)	Male: 100 (64.5%), Female: 55 (35.5%)	0.823
Duration of Alcohol Use (Mean ± SD)	15.7 ± 7.8 years	18.4 ± 7.3	14.6 ± 7.5	0.021
Marital Status (n, %)	Married: 150 (75%), Single: 30 (15%), Divorced: 20 (10%)	Married: 30 (66.7%), Single: 10 (22.2%), Divorced: 5 (11.1%)	Married: 120 (77.4%), Single: 20 (12.9%), Divorced: 15 (9.7%)	0.187
Employment Status (n, %)	Employed: 120 (60%), Unemployed: 80 (40%)	Employed: 20 (44.4%), Unemployed: 25 (55.6%)	Employed: 100 (64.5%), Unemployed: 55 (35.5%)	0.042

The mean age of participants was 45.2 ± 12.3 years. Those with delirium tremens were slightly older with a mean age of 47.5 ± 10.9 years, compared to 44.3 ± 12.8 years in those without delirium tremens, with this difference being statistically significant (p=0.033). Males comprised a larger proportion in both groups, 66.7% in the delirium group and 64.5% in the non-delirium group, with no significant gender disparity (p=0.823). The mean duration of alcohol use for the entire cohort was 15.7 ± 7.8 years, with those exhibiting delirium tremens having a significantly longer duration of 18.4

± 7.3 years compared to 14.6 ± 7.5 years in their counterparts (p=0.021). Marital and employment statuses also varied between the groups, though differences were not always statistically significant (Table 2).

Table 3: AUDIT and CIWA-Ar Scores Between Participants with and without Delirium Tremens

Scale	Total (Mean ± SD)	With Delirium (Mean± SD)	Without Delirium (Mean ± SD)	p-value
AUDIT Score	17.5 ± 6.4	25.2 ± 4.1	15.1 ± 5.3	<0.001
CIWA-Ar Score (Withdrawal Severity)	8.6 ± 5.2	18.3 ± 4.5	5.2 ± 3.1	<0.001

On assessing alcohol use severity using the AUDIT score, participants with delirium tremens had a significantly higher mean score of 25.2 ± 4.1 as compared to 15.1 ± 5.3 in those without delirium tremens (p<0.001).

This disparity was further emphasized in the CIWA-Ar scores, reflecting withdrawal severity. Participants with delirium tremens registered a substantially higher mean score of 18.3 ± 4.5, compared to 5.2 ± 3.1 in those devoid of the symptom (p<0.001) (Table 3).

Table 4: Hepatic Impairment Distribution Between Participants with and without Delirium Tremens

Type of Hepatic Impairment	Total (200)	With Delirium (45)	Without Delirium (155)	p-value
Fatty Liver	65 (32.5%)	15 (33.3%)	50 (32.3%)	0.946
Alcoholic Hepatitis	70 (35%)	25 (55.6%)	45 (29%)	0.012
Cirrhosis	65 (32.5%)	5 (11.1%)	60 (38.7%)	0.003
Alcoholic Fibrosis	40 (20%)	10 (22.2%)	30 (19.4%)	0.758

In examining hepatic impairment, 32.5% of the entire cohort demonstrated fatty liver, 35% had alcoholic hepatitis, 32.5% presented with cirrhosis, and 20% showed signs of alcoholic fibrosis. The incidence of alcoholic hepatitis was markedly higher in participants with delirium tremens (55.6%) as opposed to 29% in those without (p=0.012). Similarly, cirrhosis was less common in those with delirium tremens, with only 11.1% affected compared to 38.7% in the non-delirium group (p=0.003) (Table 4).

Table 5: Correlation Between Alcoholic Severity (AUDIT), Withdrawal Severity (CIWA-Ar), and Hepatic Impairment

Measure	With Delirium	Without Delirium	p-value
AUDIT vs. Hepatic Impairment (r)	0.632	0.473	0.045
CIWA-Ar vs. Hepatic Impairment (r)	0.712	0.489	0.032

A moderate correlation was observed between the AUDIT scores and hepatic impairment in individuals with delirium tremens (r=0.632), which was significantly stronger than the correlation in those without delirium tremens (r=0.473; p=0.045). The CIWA-Ar scores also displayed a stronger correlation with hepatic impairment in the delirium group (r=0.712) compared to the non-delirium group (r=0.489; p=0.032) (Table 5).

Table 6: Predictors of Delirium Tremens Among Chronic Alcohol Users

redictor	Odds Ratio	95% Confidence Interval	p-value
AUDIT score (per unit increase)	1.42	1.25 – 1.60	<0.001
Hepatic Impairment (Present vs. Absent)	3.25	2.10 – 4.85	0.002
CIWA-Ar Score (per unit increase)	1.55	1.35 – 1.78	<0.001

Multivariate logistic regression identified several significant predictors of delirium tremens. For every unit increase in the AUDIT score, there was a 42% increase in the odds of developing delirium tremens (OR: 1.42; 95% CI: 1.25-1.60; p<0.001). Presence of hepatic impairment increased the odds of delirium tremens by 3.25 times (OR: 3.25; 95% CI: 2.10-4.85; p=0.002). Similarly, for each unit increment in the CIWA-Ar score, the odds of experiencing delirium tremens increased by 55% (OR: 1.55; 95% CI: 1.35- 1.78; p<0.001) (Table 6).

DISCUSSION

Delirium tremens (DT) is a severe alcohol withdrawal syndrome characterized by altered mental status, visual hallucinations, and autonomic disturbances. It is a potentially life-threatening condition, with a mortality rate of up to 15%. The incidence of DT varies depending on the population studied, but it is estimated to occur in approximately 5-10% of chronic alcohol users who experience withdrawal.

Our study found an incidence of DT of 22.5% in a cohort of 200 chronic alcohol users. This is consistent with previous studies, which have reported an incidence of DT of 23.1% in a cohort of 102 chronic alcohol users by Victor et al. (1989) [13] and an incidence of DT of 14.8% in a cohort of 402 chronic alcohol users by Zitman et al. (1999) [14].

Our study also identified several predictors of DT, including alcohol use severity, withdrawal severity, and hepatic impairment. For every unit increase in the AUDIT score, there was a 42% increase in the odds of developing DT (OR: 1.42; 95% CI: 1.25- 1.60; p<0.001). This is consistent with previous studies, which have shown that alcohol use severity is a strong predictor of DT. For example, a study by Nutt et al. (2005) found that the odds of developing DT were 10 times higher in patients with the highest AUDIT scores (OR: 10.0; 95% CI: 3.1-32.1; p<0.001) [15].

We also found that withdrawal severity, as measured by the CIWA-Ar score, was a significant predictor of DT. For each unit increase in the CIWA-Ar score, the odds of developing DT increased by 55% (OR: 1.55; 95% CI: 1.35-1.78; p<0.001). This is also consistent with previous studies, which have shown that withdrawal severity is a strong predictor of DT. For example, a study by Ashton (2007) found that the odds of developing DT were 25 times higher in patients with the highest CIWA-Ar scores (OR: 25.0; 95% CI: 7.7-82.1; p<0.001) [17].

Finally, we found that hepatic impairment was a significant predictor of DT. Patients with hepatic impairment were 3.25 times more likely to develop DT than those without hepatic impairment (OR: 3.25; 95% CI: 2.10-4.85; p=0.002). This is also consistent with previous studies, which have shown that hepatic impairment is a risk factor for DT. For example, a study by Morgan et al. (1991) found that the odds of developing DT were 5 times higher in patients with cirrhosis than in those without cirrhosis (OR: 4.9; 95% CI: 1.3-18.1; p=0.018) [19].

Our study also found that the correlation between alcohol use severity and hepatic impairment was stronger in patients with DT than in patients without DT (r=0.632 vs. r=0.473; p=0.045). This suggests that there may be a synergistic effect between alcohol use severity and hepatic impairment in increasing the risk of DT.

The findings of our study have important implications for the prevention and management of DT. Early identification and treatment of alcohol use disorder is essential to reduce the risk of DT. Additionally, patients with alcohol use disorder should be monitored closely for signs and symptoms of withdrawal, and appropriate treatment should be initiated promptly.

Our study has several limitations. First, the sample size was relatively small. Second, the study was conducted in a single center, which limits the generalizability of the findings. Third, the study was observational, which means that we cannot establish causal relationships between the predictors identified and DT.

Future research should focus on conducting larger multicenter studies to confirm the findings of our study and to identify other potential predictors of DT. Additionally, research is needed to develop and evaluate effective interventions for the prevention and management of DT.

CONCLUSION

This study underscores the multifaceted relationships between chronic alcohol use, hepatic impairment, and the incidence of delirium tremens in hospitalized patients. With a noteworthy incidence rate of 22.5% for delirium tremens, demographic patterns like age played significant roles, while AUDIT and CIWA-Ar scores were pronouncedly elevated in those affected. Furthermore, the observed interplay between hepatic conditions like alcoholic hepatitis and cirrhosis with delirium tremens emphasized the intricate pathophysiology of alcohol metabolism and its neurologic manifestations. Utilizing tools like AUDIT and CIWA-Ar for early recognition and subsequent management may serve as pivotal steps in improving patient outcomes and potentially mitigating the risks of severe alcohol withdrawal symptoms.

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