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Original Article

Alcoholism and Socioeconomic Status among Patients with Hepatic Encephalopathy in Association with Increased Mortality

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Abstract

Background: Hepatic encephalopathy (HE) is a complex neuropsychiatric disorder indicated by a deterioration in the functioning of hepatocytes. Impaired brain function is observed in advanced alcoholic liver disease particularly manifesting as HE. The pathophysiology of alcohol-related HE remains unclear. Accordingly, this study aimed to assess alcoholism and socioeconomic status of patients with liver disease compared with stages of HE.

Methods: This cross-sectional study was conducted on 62 alcoholic patients who have been consuming alcohol for more than 14 years. Patients were recruited based on the assessment of clinical symptoms and diagnosed according to the MELD and Child-Pugh scoring systems.

Findings: Descriptive statistics including demographic details and clinical features of patients were classified based on alcoholism and socioeconomic status. Patients belonging to the lower- and middle-income classes were more in number with a mean age of 46.66±10.21 and 47.14±6.36 years, respectively compared to upper-middle- and upper-income classes. The amount of alcohol intake was 116.59±45.60 in the middle class and 110.0±62.45 in the upper class.

Conclusion: Increased progression of HE leads to a rise in the mortality rate due to higher consumption of alcohol. HE is a severe complication in alcohol-related liver cirrhosis that contributes to impaired cognitive function in patients.

Keywords: Alcoholism, Liver disease, Social class, Hepatic encephalopathy, Mortality

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Introduction

Hepatic encephalopathy (HE) is a neurological condition distinguished by mental impairments, stemming from both vascular anomalies and liver disease. Typically linked with decompensated cirrhosis, this condition presents a wide clinical range, covering modest cognitive deficits to severe coma. Decreased cognitive function is observed in advanced alcohol-related liver disease (ALD). The pathogenesis of HE causing brain dysfunction in ALD remains unknown. In cases of severe coma, differentiating the effects of brain edema, reduced cerebral perfusion, and reversible impairment of neurotransmitter systems becomes considerably problematic. Furthermore, these events commonly cross, particularly in models imitating severe hepatic damage, and such abnormalities may be responsible for HE development.[1,2] In severe stages of liver disease, high blood ammonia levels function as a direct neurotoxin. This mechanism comprises changes in brain metabolites, variations in cerebral blood flow, and the heightened production of inflammatory cytokines, all of which have a direct influence on brain tissue.[3] Patients with liver cirrhosis are immunocompromised, which results in increased activity of circulating pro-inflammatory mediators directly related to impaired cognitive abilities and neuronal electrical activity during disease progression.[2] Concomitant disorders such as hyponatremia, sepsis, renal dysfunction, thiamine deficiency, and diabetes mellitus have been regarded as an additional cause of neural damage in individuals with liver disease.[2,3]

The incidence of HE increased from 11.6% to 40% in 5 years. Around 21% to 33% of patients with cirrhosis exhibit neurological symptoms leading to HE.[4] Moreover, low concern for the treatment of HE may lead to reduced quality of life, and driving difficulties with increased mortality. The prevalence of HE during cirrhosis diagnosis is 10%-14%. Liver failure due to alcohol abuse significantly impacts HE manifestation.[2,4] In developed countries, liver disease is prevalent and the fifth most common disease. The observed increased mortality is due

to ALD, non-alcoholic fatty liver disease, chronic hepatitis C, and other etiological factors. HE is observed in those who experience complications before the diagnosis of chronic liver disease.[5]

Alcohol acts as a direct neurotoxin. The post-mortem material/tissue from brain banks situated in North America and Europe showed a higher incidence of neuronal injury due to alcoholic liver cirrhosis which is more compared to other etiologies. Hyperammonemia is deleterious to the immune system, muscles, and liver. Altered patients have varying sensitivities to the same amount of ammonia. Inflammation in the liver worsens systemic inflammation, thereby leading to neuroinflammation. Oxidative stress is common in cirrhosis, with higher permeability to reactive oxygen species. The release of reactive oxygen species and neutrophil dysfunction are observed during hyperammonemia which trigger inflammation and oxidative stress causing an increasingly deleterious effect on the brain. HE severity can be graded and categorized into HE stages using West Haven criteria.[6] Pathophysiology of HE is a complex entity that involves agents like ammonia, manganese deposition in the basal ganglia, benzodiazepine-like compounds, and inflammatory cytokines.[7] The suppressed variability in patients with HE is due to increased fast beta activity in patients with alcoholic liver disease. Alcoholic liver disease increases the risk of subdural hematoma despite acute-on-chronic subdural hematoma.[8] Patients with lower socioeconomic status show increased mortality due to alcohol abuse rate compared to patients with high socioeconomic status.[9] The objective of this study was to analyze the laboratory and clinical features of chronic alcoholic patients with HE based on their socioeconomic status and various stages of HE.

Methods

The present study was conducted in the Department of General Medicine at Aarupadai Veedu Medical College and Hospital in Puducherry, India. This cross-sectional study aimed to examine and comprehend the features of alcoholic patients. The study included 62 participants who had been diagnosed with chronic alcoholism for more than 15 years. The criteria for participation included individuals aged 18 years and above, with a confirmed diagnosis of alcoholic liver cirrhosis verified by both clinical symptoms and the MELD score. This study encompassed a larger research-related body of evidence, lasting over a period of two years, from the commencement of data gathering in January 2020 to its completion in December 2021. The extensive analysis of this group of alcoholic patients provides useful insights into the intricacies of alcohol-related liver cirrhosis. The study was conducted through a scoring/grading to assess the severity of HE progression in alcoholism patients with alcohol-related liver cirrhosis. The study participants, who had a history of chronic alcohol consumption, were randomly classified based on the duration of alcohol intake.

The patients were recruited based on the inclusion criteria according to clinical and diagnostic parameters such as blood urea, ammonia, potassium, and systolic and diastolic levels (mm Hg) using the MELD score. The patients with ascites, portal hypertensive bleeding, and HE were included. Patient-related data on age and gender were collected, and the Child-Pugh scoring system was used to diagnose ALD, cirrhosis, and the etiology of the liver disease. Besides, West Haven Criteria were applied to assess the psychological state of HE (Table 1).[10] Written informed consent was obtained from all study participants, and the institutional human ethical clearance was also obtained before the start of the study. The demographic details of all study participants and data on their socioeconomic status were collected by filling out a case record form (proforma).

The collected data were analyzed using SPSS statistical software (version 15). The data on categorical variables were represented as mean and standard deviation. A 95% confidence interval was considered for categorizing various pathological conditions of alcoholic patients. Median and interquartile ranges for scoring and grading methods were also constructed.

Results

The mean age of the participants was 47.0 ± 6.6 years (range: 18-55). Table 2 presents descriptive statistics for clinical and demographic information of patients, arranged depending on their socioeconomic status. Patients belonging to the lower- and middle-income classes were more in number with a mean age of 46.66 ± 10.21 and 47.14 ± 6.36, respectively compared to upper-middle- and upper-income classes.

The evaluation of alcohol use indicated different levels for the middle and higher classes, with reported values of 116.59 ± 45.60 and 110.00 ± 62.45, respectively. The mean blood urea of lower-income patients was 52.66 ± 15.01, mean serum potassium was 3.93 ± 0.87, and the mean value of ammonia was 62.66 ± 26.31. The upper-class patients showed a mean blood urea of 49.33 ± 11.93, serum potassium of 4.03 ± 0.75, and ammonia of 65.00 ± 28.48 (Table 2).

Table 3 represents the clinical features of patients categorized based on the grading of HE. Most of the alcoholic cirrhotic patients with a mean age of 45.40 ± 6.28 belonged to stage 4 of HE. The ethanol intake in grams per day ranged from 52.60 ± 10.44 to 138.86 ± 16.67. The quantity of alcohol also increased in stage 4 compared to stage 0 of HE.

The analysis of ammonia levels indicated different values, measuring 37.11 ± 3.14 in stage 0 and 93.20 ± 7.02 in stage 4 of HE. Noteworthy is the obvious confound

Table 1. West Haven criteria10 for selecting alcoholism patients↑

Grade	Definition
Grade-0	No symptoms
Grade-1	Mild unawareness, euphoria, or anxiety combined with a shorter attention span and poorer performance in supplementary activities
Grade-2	Lethargy or apathy coupled with slight confusion about time or location, modest personality changes, improper conduct, and reduced performance in subtraction activities
Grade-3	Transitioning from somnolence to a semi-stupor state, with receptivity to verbal cues, substantial bewilderment, and extreme disorientation
Grade-4	No response or hepatic coma

Table 2. Clinical features and socioeconomic status of patients with alcoholic liver disease

Clinical features	Economic status				
	Coolie (n=6)	Lower class (n=3)	Middle class (n=47)	Upper-middle class (n=3)	Upper class (n=3)
Age (Y)	49.83±6.27	46.66±10.21	47.14±6.36	39.66±8.39	46.66±6.11
Abdominal girth (cm)	34.00±6.32	39.00±2.65	36.76±4.27	39.66±3.21	36.33±1.53
Waist: Hip ratio (cm)	0.98±0.10	1.1±0.10	1.00±0.11	1.1±0.0	1.06±0.15
Ethanol intake per day (g)	82.84±32.63	86.79±49.27	91.99±35.98	142.02±0.0	86.79±49.27
Quantity of alcohol per day (mL)	105.00±41.35	110.00±62.45	116.59±45.60	180±0.0	110.00±62.45
Blood sugar (mg/dL)	106.33±10.48	108.33±17.90	109.14±23.21	128.66±21.39	116.00±22.72
Blood urea (mg/dL)	59.33±7.61	52.66±15.01	54.14±11.00	61.66±4.51	49.33±11.93
Serum potassium (mEq/L)	3.96±0.52	3.93±0.87	3.89±0.57	3.2±0.0	4.03±0.75
Ammonia (μmol/L)	62.33±24.61	62.66±26.31	66.19±21.55	90±2.65	65.00±28.48
Systolic pressure (mm Hg)	126.66±5.16	115.00±18.03	125.74±15.00	126.66±25.17	116.66±5.77
Diastolic pressure (mm Hg)	85.00±5.48	80.00±10.00	84.36±7.19	83.33±11.55	83.33±5.77
MELD score (points)	29.00±0.89	29.00±1.00	29.00±1.64	30.66±0.58	29.00±1.00

Table 3. Clinical features of HE stages in alcoholic liver disease

Clinical Features	HE Stages				
	Stage-0 (n=9)	Stage-1 (n=4)	Stage-2 (n=14)	Stage-3 (n=15)	Stage-4 (n=20)
Age (y)	45.22±6.69	44.0±9.66	47.07±6.23	50.93±5.68	45.40±6.28
Abdominal girth (cm)	39.33±2.45	35.75±7.41	36.21±4.17	35.60±5.03	36.95±3.86
Waist: Hip ratio (cm)	1.06±0.10	1.03±0.12	0.96±0.11	1.03±0.13	1.01±0.10
Ethanol intake per day (g)	52.60±10.44	47.34±0.00	69.32±6.33	90.47±14.57	138.86±16.67
Quantity of alcohol per day (mL)	66.67±13.23	60.00±0.00	87.86±8.02	114.67±18.46	176.00±21.13
RBS (mg/dL)	104.44±25.85	105.25±32.24	102.07±16.53	112.33±20.18	117.60±21.74
BU (mg/dL)	42.78±6.92	47.25±1.71	46.64±5.84	59.47±6.55	63.65±8.03
Potassium (mEq/L)	4.79±0.15	4.45±0.39	4.20±0.27	3.68±0.14	3.28±0.18
Ammonia (μmol/L)	37.11±3.14	47.50±6.19	52.71±8.95	67.47±8.06	93.20±7.02
SP (mm Hg)	123.89±13.64	117.50±26.30	126.43±13.93	128.67±8.34	123.0±16.89
DP (mm Hg)	85.56±8.46	87.50±5.0	80.36±4.99	86.0±8.28	84.0±6.81
MELD score (points)	27.44±1.33	28.0±0	28.07±1.07	29.80±1.32	30.20±0.77

Abbreviations: HE, Hepatic encephalopathy; RBS, random blood sugar; BU, blood urea; SP, systolic pressure; DP, diastolic pressure.

found in ammonia levels at stage 4 compared to the baseline values in stage 0 of HE. This study underlined the probable link between progressing phases of HE and a rise in ammonia contents (Table 3 and Figure 1).

Furthermore, the relation between baseline laboratory, clinical investigations, and Child-Pugh score was assessed and the severity of HE elevated in chronic alcoholic liver disease. The Child-Pugh score showed a 95% confidence interval of alcohol intake in grams per day particularly with West Haven criteria and in baseline of encephalopathy. The allocation of the participants based on a pathological condition such as ascites is also depicted in Figure 2.

Discussion

The present study found a strong association between ammonia and the development of HE in ALD patients. The MELD score was utilized for differentiating

cirrhotic patients and West Haven criteria was used for diagnosing HE. Moreover, the results showed there was a clear correlation between alcohol abuse and heightened development of HE in cirrhotic patients. Although more than 75% of patients reported active chronic alcoholism, particularly in a cohort aged under 47, there was a notable increase in mortality rate among these patients with alcoholic liver cirrhosis progressing to HE. The most common cause of death was related to cirrhosis complications during end-stage liver diseases such as ascites and HE.

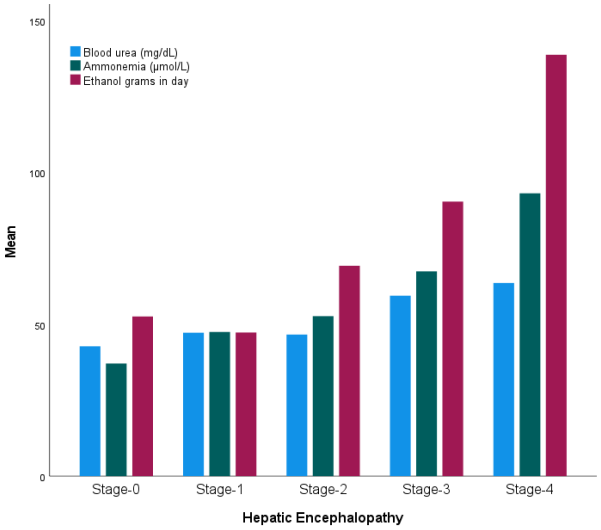

Figure 1. Mean values of blood urea, ammonia, and ethanol intake grams per day in patients with alcoholic liver disease differentiated by hepatic encephalopathy stages

The end-stage liver disease is commonly observed in older patients and develops into HE due to chronic alcohol intake. Previous studies reported that the mortality rate is significantly high in middle-aged patients.[11-13] The Centers for Disease Control (CDC) demonstrated an increase in incidence, prevalence, and mortality of alcoholic cirrhosis due to a higher intake of ethanol daily into the body which worsens liver function. This study confirmed that the incidence and development of HE in chronic alcoholic patients are higher compared to other etiologies.

The present study reported that HE progression was seen at the age of 47 years. Tapper and Parikh conducted an observational study among people aged 25-34 years and showed increased mortality in chronic alcoholic patients.[14] Alcoholic liver disease is an important contributor to HE development where decreased excretion and increased serum levels of ammonia can be observed in the human body due to liver dysfunction. The current study confirmed the findings of previous studies describing the relationship between concentrations of ammonia and the progression of HE.[2,15] Moreover, in alcohol-related liver cirrhosis, there exists a positive relation between ammonia levels, further progression to HE, and cirrhosis of liver.

Conclusion

This study demonstrated that the progression of HE patients with alcoholic liver cirrhosis leads to a rise in the mortality rate. HE is a severe complication of alcoholic liver cirrhosis that contributes to cognitive dysfunction in patients. Damaged liver in HE could gradually eliminate

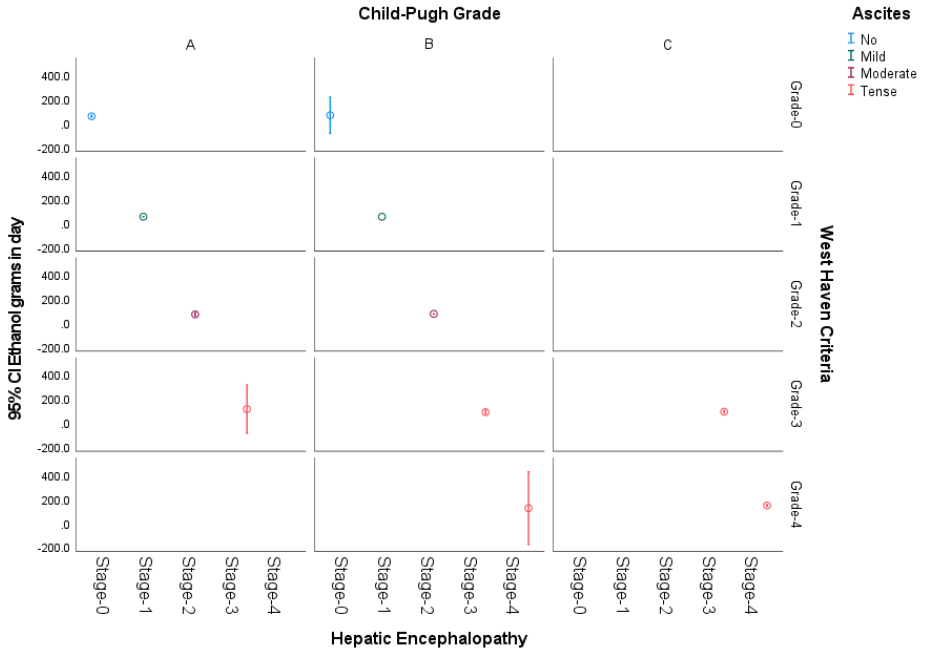

Figure 2. Ethanol consumption in alcoholic liver disease patients: A 95% confidence interval analysis of Child-Pugh score, West Haven criteria, hepatic encephalopathy stages, and ascites

neurotoxic chemicals such as ethanol, manganese, and ammonia from the blood. As a result, these neurotoxins may enter the brain and exert various harmful effects. The treatment of HE in alcoholism patients with liver damage relies on lower blood ammonia concentrations. Therefore, new therapeutic approaches are required to treat HE.

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Authors' Contribution
Conceptualization: Prabhudas Nelaturi, Sangeetha P Kadamani, Ravikumar Sambandam.
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Methodology: Prabhudas Nelaturi, Sangeetha P Kadamani, Ravikumar Sambandam.
Project administration: Prabhudas Nelaturi.
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Writing–review & editing: Prabhudas Nelaturi, Sangeetha P Kadamani, Ravikumar Sambandam.

Competing Interests
None.

Ethical Approval
The Institutional Research Committee of Aarupadai Veedu Medical College and Hospital approved all procedures carried out in this study.

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