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STUDY OF CLINICAL SPECTRUM AND ITS PRECIPITATING FACTORS OF HEPATIC ENCEPHALOPATHY IN CIRRHOSIS OF LIVER

Rahul Tarigopula[1], Jayannan Jayasenan[2], Hareesh Arumugam[3], Anbarasu Duraisamy[4*].

[1,2,3,4*]Department of General Medicine, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research (Deemed to be University), Kanchipuram, Tamil Nadu, India.

***Corresponding author:** Dr. Anbarasu Duraisamy
*Professor and Head of the Department, Dept. Of General Medicine**,** Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research (Deemed to be University), Kanchipuram, Tamil Nadu, India.

Abstract
Hepatic encephalopathy (HE) is a serious neuropsychiatric complication of liver cirrhosis characterized by a spectrum of cognitive and motor disturbances. It primarily results from the accumulation of neurotoxins, especially ammonia, due to impaired hepatic clearance. This observational study aimed to assess the clinical presentation, common precipitating factors, and their relationship with outcomes in patients with cirrhosis-related HE. Conducted at Meenakshi Medical College and Research Institute between December 2023 and May 2024, the study enrolled 50 patients diagnosed with HE. Clinical history, examination findings, laboratory results, and imaging were recorded. HE was graded using the West Haven classification, and liver function was assessed with the Child-Pugh score. Among the 50 participants, 68% were male, with most aged between 41 and 60 years. Constipation (42%), gastrointestinal bleeding (28%), infections (24%), and hyponatremia (26%) were the most common precipitating factors. A majority of patients presented with advanced HE, with grade III in 30% and grade IV in 28%. Mortality was highest in patients with grade IV HE (79%), with infections and gastrointestinal bleeding being the leading contributors. The findings underscore that HE frequently affects middle-aged males with advanced liver disease and that early identification and management of reversible triggers—particularly infections, gastrointestinal bleeding, and electrolyte disturbances—are crucial in improving patient outcomes. Timely interventions may significantly reduce both morbidity and mortality associated with HE in cirrhotic patients.

Keywords: Hepatic encephalopathy, cirrhosis, precipitating factors, West Haven classification, Child-Pugh score, hyperammonaemia, mortality, infections, gastrointestinal bleeding, electrolyte imbalance.

Introduction

Hepatic encephalopathy (HE) is a complex and multifactorial problem in patients with liver cirrhosis, resulting in significant clinical and socioeconomic burden. The problem to be solved is the unpredictable onset and progression of HE, often influenced by multiple reversible triggers.

Liver disease represents a significant healthcare burden in developing countries like India, where chronic liver conditions are major contributors to both morbidity and mortality. Among the complications associated with cirrhosis, hepatic encephalopathy (HE) stands out as one of the most serious and potentially life-threatening neuropsychiatric manifestations. It results from liver dysfunction in the absence of primary neurological disease, leading to a range of cognitive and motor disturbances. According to World Health Organization data, liver-related mortality accounts for approximately 2.95% of all deaths in India, placing it among the top causes of death nationally [10]. Recent population-based studies highlight a rising trend in cirrhosis-related complications, with hepatic encephalopathy contributing significantly to hospitalizations and healthcare costs in tertiary centres across Asia [11].

HE, also referred to as portosystemic encephalopathy, is a reversible complication of cirrhosis that affects neurocognitive performance [1,12]. Clinical manifestations can range from subtle behavioural changes to profound coma. Even minimal or covert HE can significantly impair daily functioning and quality of life [12,13]. Estimates suggest that approximately 70% of individuals with liver cirrhosis experience subclinical HE, while 30–45% develop overt manifestations [1]. The primary mechanism involves the accumulation of neurotoxic substances—particularly ammonia—due to impaired hepatic clearance and portosystemic shunting [2,4].

Ammonia, produced in the gastrointestinal tract through bacterial metabolism of nitrogenous compounds, typically undergoes hepatic detoxification. However, in cirrhotic individuals, reduced liver function and the development of portosystemic collaterals lead to systemic accumulation of ammonia, which crosses the blood-brain barrier and disrupts cerebral function [2,4,6]. While hyperammonaemia is a recognized hallmark of HE, its correlation with clinical severity remains inconsistent across studies, suggesting additional contributory mechanisms such as inflammation and altered gut microbiota [13,14]. Emerging research indicates that systemic inflammation, endotoxemia, and microbiome alterations play synergistic roles in the pathogenesis of HE, thereby opening avenues for non-ammonia-targeted therapies [13,14]. Although therapeutic strategies such as lactulose, rifaximin, and supportive care are available, their effectiveness may be limited by late presentation, recurrence, and incomplete reversal of symptoms.

Despite improvements in diagnostic capabilities and therapeutic approaches, managing HE remains a clinical challenge. Its presentation is heterogeneous, and timely recognition of early symptoms is often difficult. The West Haven criteria are widely used to categorize HE severity, ranging from grade I (mild confusion) to grade IV (coma), and remain a cornerstone for clinical staging and treatment decisions [1,7]. Current strategies, though standardized, face limitations in predicting patient outcomes and tailoring individual therapy plans. In parallel, the Child-Pugh scoring system provides a comprehensive assessment of liver function, classifying cirrhosis severity and correlating with risk of HE [1].

A wide array of precipitating factors can exacerbate HE or trigger its onset, many of which are reversible. Gastrointestinal bleeding, systemic infections, electrolyte imbalances, constipation, and high-protein intake are among the most commonly implicated [15–18]. Identifying and correcting these triggers early can prevent progression to higher grades of encephalopathy and reduce associated morbidity and mortality [19,20]. Past achievements in HE management include improved staging systems and pharmacological options; however, gaps remain in individualized risk assessment and early diagnosis.

Given the high burden of cirrhosis and its neurological complications in India—particularly among middle-aged males with alcohol-related liver disease—it is crucial to evaluate the clinical characteristics and triggers of HE in this population. This study was therefore designed to assess the clinical spectrum of hepatic encephalopathy in cirrhotic patients, identify prevalent precipitating factors, and examine their association with disease severity and outcomes. The findings aim to enhance clinical vigilance and support timely, targeted management strategies for this debilitating but reversible condition. The novelty of this study lies in its focus on a single-centre MICU population in a South Indian tertiary hospital, highlighting localized precipitating factors and severity correlation.

Materials and Methods

This observational study was conducted at Meenakshi Medical College and Research Institute over a six-month period, from December 2023 to May 2024. Patients presenting with hepatic encephalopathy (HE) in the context of liver cirrhosis were included.

Inclusion Criteria

- Patients aged above 18 years, irrespective of sex.
- Patients presenting with clinical symptoms and signs of hepatic encephalopathy associated with cirrhosis of the liver due to any cause.

Exclusion Criteria

- Patients below 18 years of age.
- Patients diagnosed with acute fulminant hepatitis or non-cirrhotic portal hypertension.

Data Collection

A total of 50 patients who met the inclusion criteria were enrolled in the study.
Data were collected using a structured proforma. Detailed clinical history was obtained, including symptoms such as fever, gastrointestinal bleeding (hematemesis/melena), constipation, diarrhea, vomiting, recent high protein intake, trauma, surgery, and paracentesis. Medication history included the use of diuretics, sedatives, tranquilizers, and NSAIDs. Previous hospital admissions were also recorded.

Comprehensive clinical examinations were performed, assessing for signs including fever, jaundice, dehydration, anemia, pedal edema, asterixis, fetor hepaticus, and ascites. HE severity was graded using the West Haven criteria, while liver function was assessed using the Child-Pugh score.

Investigations

All patients underwent the following laboratory and radiological investigations:

- Hematological parameters: Complete hemogram
- Renal function tests: Blood urea and serum creatinine
- Metabolic parameters: Random blood sugar
- Coagulation profile: Bleeding time (BT), clotting time (CT), prothrombin time (PTT), international normalized ratio (INR)
- Serum electrolytes
- Liver function tests (LFTs)
- Urine analysis: Routine and microscopy
- Radiological assessments: Chest radiograph and abdominal ultrasound.

Statistical Analysis

Data were analysed using SPSS version 22. Descriptive statistics were used to summarize findings. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean ± SD. Statistical tests were applied appropriately to examine relationships between HE severity and precipitating factors.

Ethical Considerations

Ethical approval was obtained, and informed consent was secured from all participants in accordance with the Declaration of Helsinki.

Results

Fifty patients with hepatic encephalopathy (HE) due to liver cirrhosis were included.

- **Table 1** shows the majority of patients (50%) were aged between 41 and 60 years. Males comprised 68% of the study population, reflecting a higher burden of cirrhosis-related

complications among middle-aged men. This trend may be attributed to greater alcohol consumption and related liver damage in this demographic group. These findings are consistent with demographic patterns observed in other Indian studies, where alcohol-related cirrhosis disproportionately affects middle-aged males.

Table 1: Age and Sex Distribution

Age Group (years)	Females	Males	Females (%)	Males (%)
20-40	3	7	6.0	14.0
41-60	8	17	16.0	34.0
More than 60	5	10	10.0	20.0

- **Table 2** is based on the Child-Pugh classification, 46% of patients were in Class C, 30% in Class B, and 24% in Class A. This distribution highlights that a substantial proportion of patients had advanced liver disease at presentation. This pattern also correlates with the higher severity grades of HE observed, suggesting that poor hepatic reserve is a significant contributor to neurological decompensation.

Table 2: Child-Pugh Score Distribution

Class	Child-Pugh Score	Percentage (%)
A	12	24.0
B	15	30.0
C	23	46.0

- **Table 3** described the most common precipitating factor was constipation, observed in 42% of patients. Gastrointestinal bleeding (hematemesis in 28% and melena in 22%) and infections (24%) were also prominent contributors. Electrolyte disturbances, including hyponatremia (26%) and hypokalemia (12%), along with excess protein intake (14%), diuretic use (10%), and sedative use (6%), were also identified as triggers. These findings reaffirm the predominance of modifiable factors, highlighting the opportunity for targeted prophylaxis in at-risk patients. Early identification and correction of these triggers may reduce recurrence and improve outcomes.

Table 3: Precipitating Factors of Hepatic Encephalopathy

Factor	Number of Patients (n)	Percentage (%)
Constipation	21	42.0%
Hematemesis	14	28.0%
Melena	11	22.0%
Infection	12	24.0%
Hyponatremia (Na <135)	13	26.0%
Hypokalemia (K <3.5)	6	12.0%
Excess protein intake	7	14.0%
Diuretics	5	10.0%
Sedatives	3	6.0%

- **Table 4** shows that most patients presented with advanced grades of HE. Grade III accounted for 30% of cases and grade IV for 28%, while grades I and II were seen in 24% and 18% of patients, respectively. This late-stage presentation may reflect delayed referral patterns or lack of early HE recognition at the primary care level.

Table 4: West Haven Classification

West Haven Classification	Number of Patients	Percentage (%)
I	12	24.0
II	9	18.0
III	15	30.0
IV	14	28.0

- **Table 5** describes that the highest mortality rates were seen in patients with infections (75%), followed by melena (55%), hematemesis (50%), and diuretic use (40%). Lower mortality was observed in patients with constipation, excess protein intake, and electrolyte imbalances. These data suggest that infections and gastrointestinal bleeding are particularly lethal precipitating events and warrant aggressive early management.

Table 5: Mortality According to Risk Factors

Precipitating Factors	Number of Cases	Deaths	Mortality %
Infection	12	9	75
Melena	11	6	55
Hematemesis	14	7	50
Diuretics	5	2	40
Sedatives	3	1	33
Excess protein intake	7	2	29
Hyponatremia (Na<135)	13	3	23
Constipation	21	4	19
Hypokalemia (K<3.5)	6	1	17

- **Table 6** shows that Abdominal distension was the most common symptom (68%), followed by disorientation (60%), confusion (58%), and constipation (42%). Other frequently reported symptoms included fever (24%), vomiting (20%), diarrhea (18%), hematemesis (28%), and melena (22%). The predominance of neuropsychiatric symptoms emphasizes the need to maintain a high index of suspicion for HE during initial clinical evaluation, particularly in patients without overt hepatic signs.

Table 6: Presenting Symptoms

Symptoms	Number of Cases	Percentage (%)
Abdominal Distension	34	68
Disorientation	30	60
Confusion	29	58
Constipation	21	42
Hematemesis	14	28
Coma	14	28
Fever	12	24
Melena	11	22
Vomiting	10	20
Diarrhea	9	18

- **Table 7** gives a clear correlation was observed between HE grades and mortality. Grade IV HE was associated with a mortality rate of 79%, followed by grade III (27%) and grade II (22%). This mortality gradient validates the prognostic significance of the West Haven classification and highlights the need for early grading and prompt escalation of care in advanced cases.

Table 7: West Haven Classification and Mortality

West Haven Classification	Number of Cases	Deaths	Mortality %
I	12	0	0
II	9	2	22
III	15	4	27
IV	14	11	79

Discussion

This study highlights the clinical features and precipitating factors associated with hepatic encephalopathy (HE) in patients with liver cirrhosis, emphasizing the need for early recognition and preventive strategies. The demographic distribution in our cohort, predominantly male and aged 41–60 years, aligns with broader epidemiological trends in cirrhotic populations. This male predominance is often linked to higher alcohol consumption and late healthcare-seeking behavior in this demographic, consistent with findings from previous Indian and international studies [15–17].

In terms of hepatic functional status, nearly half of the patients were categorized as Child-Pugh Class C, reflecting a pattern seen in advanced liver disease presentations. This distribution is in line with previous observations by Hameed et al. [5], reinforcing the established correlation between poor hepatic reserve and increased susceptibility to neuropsychiatric complications like HE. These findings suggest that cirrhotic patients typically present with HE only after significant decompensation has occurred, underscoring the need for better cirrhosis surveillance and earlier intervention.

Our analysis identified constipation, gastrointestinal bleeding (hematemesis and melena), infections, and hyponatremia as the most frequent precipitating factors. These triggers are commonly reported in the literature [3–5], and their high prevalence in our cohort confirms the need for vigilance in monitoring these modifiable contributors. Notably, infections and gastrointestinal bleeding were not only common but also associated with the highest mortality rates, reflecting their role in worsening hepatic metabolic stress and provoking systemic inflammatory responses.

Several prospective cohort studies have demonstrated that precipitating events—particularly infection and bleeding—can disrupt the gut-liver-brain axis, increasing the risk of acute HE episodes.

Electrolyte disturbances, particularly hyponatremia and hypokalemia, were also prominent among our cases and represent key but often underappreciated contributors to encephalopathy. These findings are in agreement with studies such as those by Abu-Assi et al. [6], who emphasized the neurocognitive impact of metabolic derangements in cirrhosis. Correcting these abnormalities early in the clinical course may help prevent progression to more advanced HE grades.

The distribution of HE severity based on the West Haven classification revealed a predominance of grade III and IV cases, suggesting that many patients present at an advanced stage. This trend is consistent with findings from Hameed et al. [5] and may reflect delayed recognition or referral, lack of community-level screening, or suboptimal outpatient monitoring of cirrhotic patients.

In addition, lack of caregiver education, financial barriers to early consultation, and poor follow-up adherence have been noted as real-world challenges contributing to late-stage HE presentations, particularly in low- and middle-income countries.

Mortality analysis further confirmed a strong association between HE severity and outcomes. Grade IV HE was associated with a mortality rate of 79%, whereas patients with grade I HE experienced no fatalities. This steep increase in mortality with advancing HE grades supports prior studies, including those by Conn et al. [21] and Sargent & Fullwood [9], which demonstrated significantly poorer prognoses in patients presenting with deeper encephalopathy. Importantly, early-stage HE may be fully reversible if promptly identified and managed.

Clinically, patients frequently presented with symptoms such as abdominal distension, altered mental status (disorientation and confusion), and signs of gastrointestinal hemorrhage. These findings further support the concept that HE often manifests neurologically before overt hepatic

symptoms become prominent, thereby requiring a high index of suspicion during initial clinical evaluation.

Overall, the results of this study reinforce the need for a proactive, multifactorial approach to the management of hepatic encephalopathy—targeting both hepatic reserve and correctable triggers. Given the reversible nature of HE in many cases, early identification and intervention remain key to reducing morbidity and improving outcomes.

Conclusion

This study demonstrates that hepatic encephalopathy (HE) predominantly affects middle-aged males with advanced stages of liver cirrhosis, particularly those classified as Child-Pugh Class C. The most common and clinically significant precipitating factors identified were constipation, gastrointestinal bleeding, infections, and electrolyte disturbances. These triggers were strongly associated with increased severity and higher mortality rates, especially in patients presenting with grade III and IV HE. Recent literature also supports that early intervention in modifiable risk factors—particularly infections and hyponatremia—can dramatically reduce HE-related readmissions and improve cognitive recovery [19,20].

Importantly, this study contributes valuable insight from a focused MICU population in South India, providing localized data that may inform region-specific management strategies. The findings underscore the need for proactive screening and early therapeutic intervention tailored to individual risk profiles. Incorporating routine assessment of precipitating factors, such as infection surveillance and electrolyte monitoring, could significantly alter the trajectory of HE progression in high-risk patients. Future multicentric studies with larger cohorts and longer follow-up are warranted to validate these findings and assess the impact of integrated preventive protocols on long-term survival. Until then, this study reinforces the importance of clinical vigilance, early diagnosis, and aggressive correction of reversible factors as cornerstones in improving HE outcomes.

Limitations

This study is subject to certain limitations. First, the relatively small sample size and single-center design may restrict the generalizability of findings to broader populations. As a result, the observed trends in precipitating factors and HE severity may not fully capture regional or global variability. Second, the study did not include advanced neuroimaging or serum biomarkers, which may have provided deeper mechanistic insight into HE pathogenesis. The analysis was also limited to inpatient data, without long-term follow-up on recurrence, rehospitalization, or neurocognitive recovery post-discharge.

Additionally, unmeasured confounders such as nutritional status, alcohol abstinence, compliance with therapy, and socioeconomic factors were not systematically evaluated. These factors could influence both the onset and reversibility of HE. Despite these limitations, the study provides clinically relevant insights into the common precipitating factors and severity distribution of HE in MICU patients, forming a strong basis for future multicentric and interventional research.

Conflict of Interest

None.

Source of Funding

None.

Authorship Contribution Statement

Rahul Tarigopula: experimentation and Writing-original draft, Jayannan Jayasenan: Review and editing Hareesh Arumugam: Review and editing, Anbarasu Duraisamy: Conceptualization and supervision.

References

1. Ferenci, P., 2017, Hepatic encephalopathy. *Gastroenterology Report (Oxford)*, 5(2), 138–147. https://doi.org/10.1093/gastro/gox013
2. Qureshi, M. O., Khokhar, N., Shafqat, F., 2014, Ammonia levels and the severity of hepatic encephalopathy. *Journal of the College of Physicians and Surgeons Pakistan*, 24(3), 160–163. https://www.jcpsp.pk/archive/2014/Mar2014/07.pdf
3. Tariq, M., Iqbal, S., Khan, N. U., Basri, R., 2009, Precipitating factors of hepatic encephalopathy. *Rawal Medical Journal*, 34(1), 95–101. https://rmj.org.pk/fulltext/27-1249409570.pdf
4. Bernal, W., Hall, C., Karvellas, C. J., Auzinger, G., Sizer, E., Wendon, J., 2007, Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. *Hepatology*, 46(6), 1844–1852. https://doi.org/10.1002/hep.21847
5. Hameed, A., Rehman, M., Saeedi, I., Shah, D., 2001, Factors precipitating hepatic encephalopathy in cirrhotic liver. *Postgraduate Medical Institute*, 15, 91–95. https://www.pgmipeshawar.edu.pk
6. Abu-Assi, S., Vlaeevie, Z. R., 2001, Hepatic encephalopathy: metabolic consequences of cirrhosis are often reversible. *Postgraduate Medicine*, 109, 123–129. https://doi.org/10.3810/pgm.2001.05.897
7. Vilstrup, H., Amodio, P., Bajaj, J. S., et al., 2014, Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by AASLD and EASL. *Hepatology*, 60(2), 715–735. https://doi.org/10.1002/hep.27210
8. Sheikh, S., 1998, Portal systemic encephalopathy in chronic liver disease: experience at People Medical College, Nawabshah. *Journal of the College of Physicians and Surgeons Pakistan*, 8, 53–55. https://www.jcpsp.pk/archive/1998/Jan1998/10.pdf
9. Sargent, S., Fullwood, D., 2006, The management of hepatic encephalopathy and cerebral edema in acute liver failure. *British Journal of Neuroscience Nursing*, 2, 448–453. https://doi.org/10.12968/bjnn.2006.2.9.21840
10. World Health Organization, 2017, Liver disease in India: WHO 2017 data. *WHO Geneva*. https://www.worldlifeexpectancy.com/india-liver-disease
11. Poordad, F. F., 2007, The burden of hepatic encephalopathy. *Alimentary Pharmacology & Therapeutics*, 25(Suppl 1), 3–9. https://doi.org/10.1111/j.1365-2036.2006.03184.x
12. Bianchi, G., Giovagnoli, M., Sasdelli, A. S., Marchesini, G., 2012, Hepatic encephalopathy and health-related quality of life. *Clinics in Liver Disease*, 16(1), 159–170. https://doi.org/10.1016/j.cld.2011.09.010
13. Bajaj, J. S., 2020, The role of microbiota in hepatic encephalopathy. *Gut Microbes*, 11(6), 1386–1399. https://doi.org/10.1080/19490976.2020.1805287
14. Hadjihambi, A., Arias, N., Sheikh, M., Jalan, R., 2017, Hepatic encephalopathy: a critical current review. *Hepatology International*, 12(Suppl 1), 135–147. https://doi.org/10.1007/s12072-017-9803-7
15. Devrajani, B. R., Shah, S. Z., Devrajani, T., Kumar, D., 2009, Precipitating factors of hepatic encephalopathy at a tertiary care hospital in Jamshoro, Hyderabad. *Journal of Pakistan Medical Association*, 59(10), 683–686. https://jpma.org.pk/article-details/1880
16. Nayak, M., Anubhaw, N., Nayak, R., 2016, Incidence of hepatic encephalopathy in cirrhosis of the liver. *International Journal of Contemporary Medical Research*, 3(12), 3528–3532. https://www.ijcmr.com/uploads/7/7/4/6/77464738/_incidence_of_hepatic_encephalopathy_in_cirrhosis_of_liver.pdf
17. Kumar, S. K. K., Sarin, S. M., Valliyot, B., Joy, V., Beevi, K., Balakrishnan, S., 2017, Study to assess the changing pattern of clinical profile and determine the prognosis in hepatic encephalopathy. *International Journal of Research in Medical Sciences*, 5(2), 424–428. https://doi.org/10.18203/2320-6012.ijrms20170165
18. Faloon, W. W., Evans, G. L., 1970, Precipitating factors in the genesis of hepatic coma. *New York State Journal of Medicine*, 70, 2891–2894. https://pubmed.ncbi.nlm.nih.gov/5482147

19. Sharma, B. C., Sharma, P., Agrawal, A., Sarin, S. K., 2021, Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. *Gastroenterology*, 160(1), 191–200.e2. https://doi.org/10.1053/j.gastro.2020.08.059
20. Bajaj, J. S., Wright, G., Dasarathy, S., Bajaj, S., 2022, The modern management of hepatic encephalopathy. *American Journal of Gastroenterology*, 117(2), 245–261. https://doi.org/10.14309/ajg.0000000000001565
21. Conn, H. O., Leiberthal, M. M., 1980, *The hepatic coma syndrome and lactulose*. Baltimore: William & Wilkins, p. 106.