

Original Article

# Precipitating Factors and Outcomes of Hepatic Encephalopathy in Patients with Chronic Liver Disease

Sana Akhtar<sup>1</sup>, Zainab Fakhar<sup>2</sup>, Samina Khan<sup>3</sup>, Abdul Razzaque Nohri<sup>4\*</sup>, Sultan Ahmed Nohario<sup>5</sup>, Muhammad Ali Memon<sup>5</sup>

<sup>1</sup>Post-Fellow Resident, Sindh Institute of Urology & Transplantation, Pakistan.

<sup>2</sup>Senior Registrar, Bahria University of Health Sciences Karachi, Pakistan.

<sup>3</sup>Postgraduate Trainee, PNS Shifa Hospital Karachi, Pakistan.

<sup>4</sup>Senior Pharmacist, Health Department, Government of Sindh-MSPH Candidate Liaquat University of Medical Health Sciences Jamshoro

<sup>5</sup>Physician General, Liaquat University of Medical and Health Science Jamshoro

\*Corresponding Author: Abdul Razzaque Nohri, Senior Pharmacist; Email: razaquenohri@gmail.com

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## ABSTRACT

**Background:** Hepatic encephalopathy (HE) is a complex neuropsychiatric condition that significantly impacts patients with chronic liver disease (CLD), leading to hospital admissions and contributing to the economic burden on healthcare systems. The condition's pathogenesis involves various precipitating factors, yet its management remains challenging due to the multifaceted nature of its presentation.

**Objective:** This study aims to identify the precipitating factors of HE in patients with CLD, assess the severity and outcomes of HE, and evaluate the correlation between precipitating factors and the severity and outcomes of HE in patients admitted to PNS Shifa Hospital, Karachi, Pakistan.

**Methods:** A descriptive cross-sectional study was conducted over six months, from February 2022 to July 2022, at the Department of Medicine, PNS Shifa, Karachi. A total of 78 patients meeting the inclusion criteria were enrolled through convenience sampling. Informed consent was obtained from each participant. The severity of liver disease was assessed using the Child-Pugh Classification, and the presence and grade of HE were determined using the West Haven criteria. Precipitating factors of HE were evaluated, and patients were followed until discharge to assess the length of hospital stay and in-hospital mortality. Data were analyzed using SPSS version 25, focusing on descriptive and inferential statistics.

**Results:** The mean age of the participants was  $48.77 \pm 13.37$  years, with the duration of CLD averaging  $3.19 \pm 1.45$  years. Hospital stays ranged from 1 to 7 days, with a median of 5.0 days. Child-Pugh classification revealed 35.9% of patients in Class A, 33.3% in Class B, and 30.8% in Class C. HE grades were distributed as follows: Grade I in 48.7%, Grade II in 24.4%, Grade III in 15.4%, and Grade IV in 11.5% of patients. In-hospital mortality was observed in 15.4% of cases. The most common precipitating factors identified were constipation (59.0%), followed by hypoglycemia (52.6%), and recent excessive paracentesis (48.7%).

**Conclusion:** The study underscores the importance of identifying and managing precipitating factors of HE in patients with CLD to mitigate the severity of HE and improve patient outcomes. Constipation, hypoglycemia, and recent excessive paracentesis were the most prevalent precipitating factors, suggesting targeted interventions in these areas could reduce the incidence and severity of HE.

**Keywords:** Hepatic encephalopathy, Chronic liver disease, Precipitating factors, Child-Pugh Classification, West Haven criteria, In-hospital mortality.

## INTRODUCTION

Hepatic encephalopathy (HE) is recognized as a complex neuropsychiatric syndrome predominantly afflicting patients with advanced liver cirrhosis (LC), and is a notable complication arising from chronic liver disease (CLD). This condition gravely affects the quality of life for both patients and their caregivers, and it stands as a prevalent cause for hospital admissions among individuals diagnosed with LC, thus placing a significant economic burden on both healthcare systems and the patients themselves (1-4). The pathophysiology behind HE, while not entirely understood, is believed to be multifactorial, involving precipitating factors such as infections, constipation, gastrointestinal (GI) bleeding, inflammation, oxidative stress, and alterations in metabolites like lactic and bile acids (5). Investigations into the precipitating factors of HE in hospitalized CLD patients have identified infections, constipation,

and GI bleeding as the most commonly reported triggers, with infection rates varying significantly across studies but generally highlighted as a primary factor (6-8).

Subsequent studies have further elucidated the complex relationship between these precipitating factors and the development and severity of HE, indicating that patients with a greater number of precipitants tend to experience a more severe form of HE and endure longer hospital stays. This correlation suggests that the synergistic impact of these factors significantly contributes to the condition's progression (11-15). In contrast, patients presenting with fewer or no precipitants have demonstrated better clinical outcomes, including reduced mortality rates and shorter durations of hospitalization, highlighting the importance of identifying and managing these factors proactively (8). Moreover, the efficacy of treatment regimens, such as the combination of lactulose with rifaximin or L-ornithine L-aspartate (LOLA) compared to lactulose alone, has been scrutinized, revealing variations in patient outcomes, particularly in terms of hospital stay length, although no significant differences were observed in mortality rates among the different treatment groups (7).

The examination of literature pertaining to HE in the context of CLD reveals a notable variance in the incidence and impact of its precipitating factors across various studies, emphasizing the critical role these factors play in both the severity and outcomes of the condition. This variability underscores the necessity for ongoing research to deepen our understanding of these precipitating factors, with the aim of refining treatment strategies and improving the prognosis for patients affected by HE.

## MATERIAL AND METHODS

The study was designed as a descriptive cross-sectional analysis and was conducted at the Department of Medicine, PNS Shifa, Karachi, Pakistan, over a six-month period from February 2022 to July 2022. The research aimed to enroll patients who met the predefined inclusion criteria during their visit to PNS Shifa. Upon recruitment, informed consent was obtained from each participant. The consent process involved a detailed explanation of the study's procedures, potential risks, and benefits, ensuring participants were well-informed before agreeing to partake in the study. This approach adhered to the ethical considerations outlined in the Declaration of Helsinki, emphasizing respect for individuals and ensuring informed consent, confidentiality, and the right to withdraw without penalty.

For the purpose of evaluating the severity of liver disease among the study population, the Child-Pugh Classification was employed, a recognized method for assessing the prognosis of chronic liver disease, primarily cirrhosis. To ascertain the presence and grade of hepatic encephalopathy (HE), the West Haven Criteria were utilized, providing a standardized measure for the clinical grading of mental status changes in HE (7, 9). Participants were meticulously evaluated for potential precipitating factors of HE, and their health outcomes were monitored up to the point of discharge from the hospital. The focus was on determining the length of hospital stay and recording any instances of in-hospital mortality (10).

Data collection was rigorously conducted, with all relevant information being meticulously documented on a proforma designed specifically for this study. This proforma facilitated the structured gathering of data, which was subsequently digitized and analyzed electronically, solely for research purposes. For the analysis of the collected data, the Statistical Package for the Social Sciences (SPSS) version 25 was utilized. This software enabled the comprehensive analysis of the data, including descriptive statistics to summarize the patient characteristics and inferential statistics to explore the relationships between precipitating factors of HE, the severity of liver disease, and patient outcomes (11, 15).

Ethical approval for the study was obtained from the institutional review board (IRB) of PNS Shifa, ensuring that the study's design and execution conformed to the highest standards of ethical research conduct. The study's adherence to ethical guidelines, coupled with the thorough methodological approach, aimed to contribute valuable insights into the precipitating factors and outcomes of HE in patients with chronic liver disease, with the ultimate goal of enhancing patient care and management strategies in this vulnerable population.

## RESULTS

In the descriptive analysis of the study sample comprising 78 participants, the Shapiro-Wilk test was utilized to assess the normality of the data distribution. Results indicated significant deviations from normality for age, duration of chronic liver disease (CLD), and length of hospital stays, with p-values all less than 0.0001 (Table 1). The average age of the participants was 48.77 years, with a standard deviation of 13.37 years. The mean duration of CLD was reported at 3.19 years (SD = 1.45), and the average length of hospital stays was 4.56 days (SD = 1.72), suggesting a wide range of disease durations and hospitalization lengths among the patients.

Table 1: Descriptive Statistics of Shapiro-Wilk Test (n=78)

Variable	Mean $\pm$ SD	P-Value
Age group	48.77 $\pm$ 13.37	<0.0001
Duration of CLD	3.19 $\pm$ 1.45	<0.0001
Hospital Stays	4.56 $\pm$ 1.72	<0.0001

Table 2: Frequency of Child-Pugh Class (n=78)

Child-Pugh Class	Frequency	Percentage
Class A	28	35.9%
Class B	26	33.3%
Class C	24	30.8%

Table 3: Frequency of HE Grades (n=78)

HE Grades	Frequency	Percentage
Grade I	38	48.7%
Grade II	19	24.4%
Grade III	12	15.4%
Grade IV	9	11.5%

Table 4: Frequency of In-Hospital Mortality (n=78)

In-Hospital Mortality	Frequency	Percentage
Yes	12	15.4%
No	66	84.6%

Table 5: Stratification of Age Group with Precipitating Factors (n=78)

Precipitating Factors	Age 18–40	Age >40	P-Value
Infection	8 (10.3%)	21 (26.9%)	0.516
Constipation	12 (15.4%)	34 (43.6%)	0.176
Hypokalemia	7 (9.0%)	20 (25.6%)	0.399
Hyponatremia	11 (14.1%)	23 (29.5%)	0.960
Hepato-renal syndrome	13 (16.7%)	24 (30.8%)	0.579
Hypoglycemia	14 (17.9%)	27 (34.6%)	0.676
GI Bleeding	7 (9.0%)	21 (26.9%)	0.318
Hepatocellular Carcinoma	6 (7.7%)	19 (24.4%)	0.295
Recent Excessive Paracentesis	14 (17.9%)	24 (30.8%)	0.377

Regarding the severity of liver disease as categorized by the Child-Pugh classification, the distribution among the study population was relatively even, with 35.9% classified as Class A, 33.3% as Class B, and 30.8% as Class C, highlighting the presence of varying degrees of liver disease severity among the participants (Table 2). This classification underscores the diversity in the clinical status of the patients enrolled in the study.

The frequency of hepatic encephalopathy (HE) grades among the participants further delineated the clinical spectrum of the condition. Grade I HE was the most common, observed in 48.7% of the patients, followed by Grade II in 24.4%, Grade III in 15.4%, and Grade IV in 11.5%, illustrating the predominance of milder forms of HE within this cohort (Table 3). This distribution provides insight into the clinical severity of HE in the study population, with nearly half of the patients experiencing the least severe form of the condition.

In-hospital mortality was recorded for 15.4% of the study participants, while the majority, 84.6%, survived their hospital stay, reflecting the serious nature of HE but also indicating a significant survival rate within this clinical setting (Table 4). This outcome variable underscores the critical need for timely and effective management strategies for patients presenting with HE.

The stratification of age groups with precipitating factors revealed no statistically significant associations between age and various precipitants of HE, such as infection, constipation, hypokalemia, hyponatremia, hepato-renal syndrome, hypoglycemia, gastrointestinal bleeding, hepatocellular carcinoma, and recent excessive paracentesis, with p-values ranging from 0.176 to 0.960

(Table 5). This analysis suggests that the impact of these precipitating factors on the development of HE is not significantly influenced by the age of the patients, indicating a broad relevance of these factors across different age groups within the CLD population.

Together, these findings illuminate the complex clinical landscape of HE among patients with CLD, highlighting the significant variability in disease severity, the range of precipitating factors involved, and the outcomes of patients hospitalized with this condition. The results emphasize the importance of comprehensive clinical assessment and management strategies tailored to the individual patient's disease severity and precipitating factors to optimize outcomes.

## DISCUSSION

The findings of our investigation into the characteristics and outcomes of hepatic encephalopathy (HE) among patients with chronic liver disease (CLD) present a comprehensive overview that aligns with and expands upon existing research in this field. The age distribution of our study participants, ranging from 18 to 65 years with a median of 51.50, closely mirrors the demographics reported in similar studies, indicating a wide age range affected by CLD and its complications. Comparable studies have reported mean ages ranging from 44.3 years (1) to 55 years (8), underscoring the variability in age distribution among CLD patients across different populations. The length of hospital stays in our study, which varied from 1 to 7 days with a median of 5.0 days, similarly reflects the findings of Poudyal S, et al. (7) and Mumtaz K, et al. (8), suggesting a generalizable pattern of hospitalization duration for HE patients across different settings.

The gender distribution in our cohort, with 62.8% male and 37.2% female patients, is consistent with the gender disparities noted in other studies, such as those by Kabir MA, et al. (1) and Devrajani BR, et al. (6), which also reported a higher prevalence of CLD and HE among males. This gender disparity highlights the need for targeted interventions and raises questions about the role of gender-specific risk factors in the pathogenesis of CLD and HE.

Our study's stratification of patients according to the Child-Pugh score and HE grades provides valuable insights into the severity of liver disease and encephalopathy among the study population, revealing a distribution across Child-Pugh classes A to C and HE grades I to IV that is broadly reflective of the clinical spectrum of the disease. This distribution aligns with findings from other researchers (1, 7, 8), although the proportions vary, reflecting differences in study populations and possibly in the criteria used for classification and grading.

In terms of in-hospital mortality, our findings of a 15.4% mortality rate among HE patients offer a crucial perspective on the outcomes of this condition, comparing favorably with higher mortality rates reported in other studies (1, 9). This variation may be attributed to differences in healthcare settings, patient management strategies, and the severity of precipitating factors.

The prevalence of precipitating factors of HE in our study, with constipation, hypoglycemia, and recent excessive paracentesis being the most common, provides a significant correlation with the existing literature, emphasizing the multifactorial nature of HE in CLD patients (6, 7, 8, 9, 10). These findings underscore the critical importance of managing these precipitating factors to prevent or mitigate the severity of HE.

Our study, while contributing valuable data to the existing body of knowledge on HE in CLD, is not without its limitations. The cross-sectional design and single-center setting may restrict the generalizability of our findings. Additionally, the study's reliance on retrospective data and the potential for selection bias highlight the need for further, large-scale, multicentric prospective studies to validate and expand upon our findings.

## CONCLUSION

In conclusion, our study reinforces the complexity of managing HE in patients with CLD, pointing to the need for a multidisciplinary approach that addresses both the precipitating factors and the underlying liver disease. Future research should focus on longitudinal assessments to better understand the progression of HE and the impact of various management strategies on patient outcomes. Moreover, our findings highlight the urgent need for public health interventions aimed at preventing CLD, particularly in regions where hepatitis B and C are prevalent, to reduce the burden of HE and improve the quality of life for affected individuals.

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