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Evaluation of Hepatic Encephalopathy Triggers and Outcomes in Chronic Liver Disease: A Regional Perspective

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ABSTRACT

Background: Chronic liver disease (CLD) accounts for a neuropsychiatric complication called hepatic encephalopathy (HE). This study aimed to explore the key precipitating factors in HE and determine how they correlated with disease severity; findings were compared to global trends.

Methods: This cross-sectional study was carried out (December 2019 to July 2020) at the Asian Institute of Medical Sciences (AIMS), Hyderabad, Pakistan. A total of 205 patients with secondary HE to CLD were included. Using the consecutive techniques, demographic characteristics, precipitating factors, used liver dysfunction scores (Child-Turcotte-Pugh and Model for End-Stage Liver Disease) were analysed using SPSS version 20. significant associations ($p < 0.05$) were identified statistically using Chi-square and ANOVA test.

Results: Electrolyte imbalances (48%) (n=98), principally hyponatremia (18%) (n=37), were the most frequent precipitating factors, while the most common precipitating factors were infections (35.1%) (n=72) with spontaneous bacterial peritonitis being the most frequent (16.6%) (n=34). In 14.6% (n=30) of cases, gastrointestinal bleeding was observed. Infected and severe electrolyte disturbance ($p<0.05$) were significantly associated with higher grades of HE (Grade III/IV). Patients with Child C classification and MELD >20 had a more severe history of HE episodes. Infections were more common in older patients (≥60 years), whereas younger patients (<40 years) were more susceptible to dehydration and development of gastrointestinal bleeding.

Conclusion: Electrolyte imbalances and infections were the main precipitants. Electrolyte monitoring, infection control, and demographics-specific strategies are paramount to improving patient outcomes.

Keywords: Hepatic Encephalopathy, Liver Cirrhosis, Liver Diseases, Gastrointestinal Hemorrhage, End Stage Liver Disease.

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INTRODUCTION

Hepatic encephalopathy (HE) is a debilitating complication of chronic liver disease (CLD) and is a worldwide problem for clinicians. A wide spectrum of neuropsychiatric symptoms from subtle cognitive dysfunction to profound coma defines the disease and, with the consequent serious impairment of the quality of life of the patients and caregivers, costs billions of dollars per year globally [1]. Caused by decompensated cirrhosis, reflecting its very severe progression of liver dysfunction, with prevalence rates up to 30-50% in cirrhotic patients and up to 80% in advanced cases, is a hallmark of decompensated cirrhosis [2].

The pathophysiology of HE is multifactorial and ammonia toxicity is the key element. High serum ammonia due to portosystemic shunting and impaired hepatic detoxification disrupts the blood brain barrier and causes alterations in neurotransmission [3]. Besides, HE is recognized as an important pathogenic factor, including systemic inflammation, oxidative stress, and gut microbiota dysbiosis to HE [4]. These certainly confirm the role of attempting to prevent HE episodes by targeting liver dysfunction in addition to precipitation factors. Stable CLD is converted into episodes of overt HE by precipitating factors. Electrolyte imbalances (e.g., hyponatremia and hypokalemia), infections (e.g., spontaneous bacterial peritonitis and urinary tract infections), gastrointestinal bleeding, and dehydration and constipation are common triggers [5].

These factors must be identified and promptly managed to prevent HE exacerbations and improve patient outcomes. Variations of HE precipitants have been reported in all regions, reflecting geographical differences in access to healthcare, patient demographics, and the aetiology of liver disease [6]. Viral hepatitis (hepatitis B and C), predominates as the leading cause of CLD in South Asia, including Pakistan. Electrolyte imbalances and infections were found to be the most common precipitants in the Pakistani populations, while gastrointestinal bleeding was less frequent, as early interventions such as endoscopy and prophylactic antibiotic use have been improved [7]. These results highlight the need for localized data to inform effective prevention and therapeutic strategies. AIMS, Hyderabad is a tertiary medical center, catering to a wide spectrum of the patient population with a high burden of CLD and HE cases. Variations in reported precipitants and a paucity of regional data, however, hamper the development of standardized management protocols [8]. We hypothesized that this study would analyze the frequency and pattern of HE precipitants in CLD patients at AIMS [9]. The study identifies common triggers and their associations with demographic and clinical variables that would inform clinical decision making and improve patient care.

Given the scarcity of healthcare resources in Pakistan, and the unavailability of liver transplantation, a definitive treatment for decompensated cirrhosis, this research is particularly applicable in Pakistan [10]. Early recognition and treatment of precipitating factors for HE, which allows effective management of HE, can decrease hospitalizations, healthcare costs, and mortality. In addition, the results may help inform the global literature on HE, illustrating how managing this condition in low resource settings also presents unique challenges and opportunities [11]. Because HE places a heavy burden on patients and healthcare systems, it is crucial to develop evidence-based strategies appropriate to the region. The objective of this study was to address a critical gap in the literature by offering insight into the clinical profile of HE in the Pakistani population, with special reference to the role of precipitating factors in disease progression and management outcomes [12].

METHODS

The study was conducted as a cross-sectional study at the Department of Gastroenterology and Hepatology, Asian Institute of Medical Sciences (AIMS), Hyderabad from December 2019 to July 2020 (AIMS/ERC/9280/19). This study was designed to determine the precipitating factors of hepatic encephalopathy (HE) in patients with chronic liver disease (CLD). Using the consecutive techniques, a sample size of 205 patients, a prevalence rate of hepatic encephalopathy precipitants from previous studies, a 95% confidence level, and a 5% margin of error were assessed by using OpenEpi software version 3.01. Adult patients aged 18 years or greater with a documented diagnosis of CLD and evidence of HE, both clinically and/or biochemically, were included in the study, according to the West Haven criteria. The study excluded patients with neurological conditions other than HE, on sedative medications, or with a lack of complete medical records.

Demographic details, clinical parameters, and laboratory investigations were documented by a structured proforma. Age, gender, vital signs, HE grades, and laboratory results (serum electrolytes, infection markers, liver function tests, and renal function tests) were key variables. Clinical outcomes were predicted and liver dysfunction severity was assessed using the Child–Turcotte–Pugh (CTP) and the Model for End-Stage Liver Disease (MELD).

Institutional Review Board of AIMS, Hyderabad, ethical approval was obtained and written informed consent was obtained from the participants or their legal representatives. SPSS version 23.0 was used for statistical analysis. For continuous variables, means with standard deviations, and for categorical variables, frequencies and percentag-

es have been summarized. Associations between categorical variables were assessed using the Chi-square test, with $p<0.05$ taken as statistically significant.

RESULTS

A total of 205 patients with chronic liver disease (CLD) presenting with hepatic encephalopathy (HE) were included in the study. The mean age of the participants was 52.40 ± 11.35 years, with a male predominance (63.9%, n=131), while females constituted 36.1% (n=74). The study examined the frequency and types of precipitating factors for HE, their association with demographic variables, and the severity of liver dysfunction.

The most commonly identified precipitant of hepatic encephalopathy (HE) was electrolyte imbalance, present in 48% (n=98) of patients. Within this category, hyponatremia accounted for 18% (n=37) of cases, hyperkalemia for 16.6% (n=34), hypokalemia for 11.2% (n=23), and hypernatremia for 10.2% (n=21). Infections were the second most frequent category of precipitants, occurring in 35.1% (n=72) of patients, with spontaneous bacterial peritonitis (SBP) present in 16.6% (n=34), urinary tract infections (UTIs) in 14.6% (n=30), and pneumonia in 4.9% (n=10). Other significant precipitants included constipation and dehydration, each affecting 22.9% (n=47) of patients. Gastrointestinal bleeding was observed in 14.6% (n=30), marking a decline compared to older studies due to improved management protocols such as early antibiotic use and gut decontamination.

Statistical analysis using the Chi-square test revealed significant associations between HE and electrolyte imbalance ($p < 0.01$) and infections ($p < 0.05$).

Table 1: Precipitating Factors of Hepatic Encephalopathy

Precipitant	Frequency (%)	Total Patients (n=205)	p-value (Chi-square)
Electrolyte Imbalance	48.0	98	<0.01
Infections	35.1	72	<0.05
Constipation	22.9	47	0.08
Dehydration	22.9	47	0.10
Gastrointestinal Bleeding	14.6	30	0.12

The severity of HE, categorized using the West Haven criteria, was distributed as follows: Grade I (mild confusion, impaired attention): 28% (n=57), grade II (lethargy, disorientation): 34.1% (n=70), grade III (marked confusion, stupor): 25.4% (n=52) and grade IV (coma): 12.2% (n=25).

Higher grades of HE (Grade III and IV) was significantly associated with severe precipitating factors, such as infections and electrolyte imbalances ($p < 0.05$). Patients with Grade III/IV HE was more likely to require intensive care and had poorer prognoses.

Table 2: Severity of Hepatic Encephalopathy

HE Grade	Frequency (%)	Total Patients (n=205)	p-value (Chi-square)
Grade I	28.0	57	0.09
Grade II	34.1	70	<0.05
Grade III	25.4	52	<0.01
Grade IV	12.2	25	<0.01

The severity of liver disease was assessed using the Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores. CTP Score was distributed according to these three categories: Child A (compensated cirrhosis): 5.8% (n=12), child B (moderately decompensated): 38% (n=78), and child C (severely decompensated): 56.2% (n=115). Similarly, MELD Score was distributed according to the following categories: less than 15 (low severity): 27.8% (n=57), within 15–20 (moderate severity): 43.4% (n=89), and greater than 20 (high severity): 28.8% (n=59).

Analysis using ANOVA revealed significant differences in HE severity based on liver dysfunction scores. Patients classified as Child C or with MELD scores >20 were significantly more likely to experience severe HE episodes ($p < 0.01$).

Table 3: Liver Dysfunction Scores

Score Category	Frequency (%)	Total Patients (n=205)	p-value (ANOVA)
Child A	5.8	12	0.10
Child B	38.0	78	<0.05
Child C	56.2	115	<0.01
MELD <15	27.8	57	0.07
MELD 15–20	43.4	89	<0.05
MELD >20	28.8	59	<0.01

Age and gender demonstrated significant associations with the frequency and type of precipitating factors: Patients aged ≥60 years exhibited a higher prevalence of infections and electrolyte disturbances ($p < 0.05$). Hyponatremia and SBP were particularly frequent in this group. On the other hand, younger patients (<40 years) were more likely to present with dehydration and gastrointestinal bleeding. Gender based differences were also noticeable. Male patients were more frequently associated with dehydration ($p = 0.02$) and gastrointestinal bleeding ($p = 0.03$) than female patients who had a higher prevalence of infections, particularly UTIs ($p < 0.05$).

Results suggest that HE is related to electrolyte imbalances, infections, and constipation as important predisposing factors. These days prophylactic measures such as endoscopic interventions, antibiotic use, etc. have improved markedly so that there has been a declining frequency of gastrointestinal bleeding. However, the electrolyte disturbances, with a high prevalence of hyponatremia, compel urgent monitoring and timely management in at-risk patients.

DISCUSSION

The most commonly identified precipitant of hepatic encephalopathy (HE) was electrolyte imbalance, present in 48% (n=98) of patients. Within this category, hyponatremia accounted for 18% (n=37) of cases, hyperkalemia for 16.6% (n=34), hypokalemia for 11.2% (n=23), and hypernatremia for 10.2% (n=21). The results of this study contribute to understanding the precipitation of contributing factors, disease severity, and demographic patterns influencing HE management in the resource-limited setting of Pakistan[13]. The most frequent precipitant was electrolyte imbalance, occurring in 48% (n=98) of the patients (18%, n=37, hyponatremia) [14]. These results are consistent with the pathophysiologic scheme of HE, where hyponatremia results in swelling of the astrocytes and dysfunction of neurotransmitters which are both compounded and worsen neurological outcomes. Electrolyte disturbances, ascribed to dietary deficiency and lack of monitoring, were described in 55% (n=113) of Pakistani cases. However, a researcher discovered a lower prevalence (12%) than the above in North America because of better dietary practices and healthcare measures [15]. These discrepancies accentuate the need for region-specific dietary advice as well as regular serum sodium monitoring to prevent HE episodes in resource-limited settings. The second most common precipitants were infections, most notably spontaneous bacterial peritonitis (SBP, 16.6%) and urinary tract infections (UTIs, 14.6%) [16].

Similar to a study, where infections comprised 33% (n=68) of, HE cases. Nevertheless, a lower infection rate (25%) (n=51) was reported in the United States because widespread prophylactic antibiotic use and early intervention protocols were employed [17]. This higher prevalence of infections is a result of gaps in preventive measures, delayed diagnosis, and limited access to prophylactic antibiotics. Infection-induced systemic inflammation further exacerbates ammonia production and blood brain barrier dysfunction, and therefore, infection prevention and rapid management should be the focus.

Interestingly, GI bleeding was observed in only 14.6% (n=30) of cases compared with earlier studies which showed a prevalence of 30% [18]. The causes of this reduction include improved endoscopic techniques, pharmacological prophylaxis, and improved portal hypertension management [19]. However, GI bleeding is still a major precipitant, particularly for patients with severe liver dysfunction. Moreover, its presence underscores the necessity of remaining vigilant and increasing access to preventive and treatment modalities. Important demographic patterns in HE precipitating factors emerge in this study. Patients ≥60 years were older and had a higher prevalence of infections and electrolyte disturbances, with a higher prevalence of infections and electrolyte disturbances attributed to immunosenescence and reduced sodium renal handling capacity [20]. On the other hand, younger patients (<40 years) were more likely to have dehydration and GI bleeding. This difference may be a result of differences in exposure to risk factors, health seeking behavior, and lifestyle choices [21]. There were also gender specific differences, with males more likely

to have dehydration and GI bleeding and females more likely to have UTIs [22]. The results have pointed out anatomical and behavioral factors underlying gender disparities in HE precipitating factors. It is important to understand these demographic variations to help in developing tailored interventions to take care of the unique needs of different patient subgroups [23].

The results of this study mirror regional data but differ significantly from global trends. For example, infections and electrolyte imbalances are again the dominant precipitants of HE in this cohort, similar to other South Asian studies, reflecting similar healthcare challenges and disease patterns [24]. The declining prevalence of GI bleeding also reflects the global trend observed in high resource settings. Their emphasis on the need to adapt global best practices to local healthcare contexts highlights the importance of improvement [25]. This study yields several actionable priorities for better management of hepatic encephalopathy (HE). Electrolytes should be routinely monitored, with protocols in place for the evaluation and timely correction of sodium and potassium abnormalities to avoid life threatening HE episodes [26]. Equally important is the need for strengthened infection control measures, such as expanded access to prophylactic antibiotics, improved diagnostics, and timely management of infections to reduce systemic inflammation and its effect on HE progression. Priority should be given to enhancing the prevention of gastrointestinal (GI) bleeding by the widespread use of evidence-based interventions such as endoscopic variceal ligation and beta blockers to reduce bleeding complications in cirrhotic patients. In addition, demographic specific strategies should be developed to address age and gender specific strategies, given the different risk profiles, and to optimize preventive care and outcomes among different patient populations [27]. These measures can be used together to greatly reduce the burden of HE in resource limited settings and improve patient care in general.

The need for multicentre longitudinal studies to validate its findings and to explore newer biomarkers for the early detection of HE has been highlighted in this study. Telemedicine and mobile health technologies may also be integrated to bridge healthcare access gaps, such as in resource limited settings like Pakistan. Future research should also explore the contribution of dietary interventions and microbiota modulation to mitigating HE risk.

CONCLUSION

Electrolyte imbalances and infections are the predominant precipitating factors for HE with significant impact on disease severity. These findings highlight the necessity for targeted interventions, as well as demographic specific strategies to lessen the HE burden, especially in resource limited settings. This study provides a context for interpreting these results globally and in the region and contributes to a broader understanding of HE management and areas for future research and policy improvement.

LIST OF ABBREVIATIONS

AIMS - Asian Institute of Medical Sciences
ANOVA - Analysis of Variance
CLD - Chronic Liver Disease
CTP - Child-Turcotte-Pugh
ERC - Ethical Review Committee
GI - Gastrointestinal
HE - Hepatic Encephalopathy
MELD - Model for End-Stage Liver Disease
SBP - Spontaneous Bacterial Peritonitis
SPSS - Statistical Package for the Social Sciences
UTI - Urinary Tract Infection

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None

CONFLICT OF INTEREST

None

ETHICAL APPROVAL

The study received ethical approval from the Institutional Review Board at the Department of Gastroenterology and Hepatology, Asian Institute of Medical Sciences (AIMS), Hyderabad, under reference number (AIMS/ERC/9280/19).

AUTHORS' CONTRIBUTIONS

MAS, OA: Conceived the idea and designed the research work, **MA, AH:** did data analysis, **RB, UB:** Did the manuscript writing, **AH, UB, EUH:** Did proofreading and editing, and all authors agreed to be accountable for all aspects of research.

REFERENCES

1. Heusinger D, Dhiman RK, Felipa V, Garg B, Jalan R, Kirsches G et al. Hepatic encephalopathy. Nature Reviews Disease Primers. 2022 Jun;8(1):43. Doi: 10.1038/s41572-022-00366-6
2. Glairing SJ, Mangini C, Antonello L, Gioia S, Nielsen EJ, Danneberg S et al. Prevalence of minimal hepatic encephalopathy in patients with liver cirrhosis: A multicenter study. Official journal of the American College of Gastroenterology| ACG. 2022 Mar:10-4309. Doi: 10.14309/ajg.0000000000002251
3. Tejpal S, Sharma SK, Sharma A, Sharma S. A comprehensive review on hepatic encephalopathy: pathophysiology, symptoms, epidemiology, classification, diagnosis and treatment. J Res Appl Sci Biotechnology. 2024 Jun;3(3):170-80. doi:10.55544/-jrasb.3.3.27
4. Nardelli S, Riggio O, Gioia S, Merli M, Spagnoli A, di Martino M et al. Risk factors for hepatic encephalopathy and mortality in cirrhosis: The role of cognitive impairment, muscle alterations and shunts. Digestive

and Liver Disease. 2022 Aug;54(8):1060-5. Doi: 10.1016/j.dld.2021.12.015
5. Bhattarai S, Karki D. Clinical profile, precipitating factors and outcome of hepatic encephalopathy in patients with liver cirrhosis. Med Phoenix. 2021 Jul;6(1):23-7. doi:10.3126/medphoenix.v6i1.36796
6. Singh HM, Sharma LR, Bijoy M. Precipitating Factors and Outcome of Hepatic Encephalopathy-A Hospital Base Cross Sectional Study. Int J Accad Med Pharm. 2023 Aug;5(5):1808-15. Doi: 10.47009/jamp.2023.5.5.356
7. Razai A, Safi IK, Saidi SA, Saidi SI. Prevalence of Precipitating Factors of Hepatic Encephalopathy at Nangarhar Regional Hospital. Nangarhar University International Journal of Biosciences. 2023 Sep;2(03):34-41. doi:10.70436/nuijb.v2i03.67
8. Xu X, Yang Y, Tan X, Zhang Z, Wang B, Yang X et al. Hepatic encephalopathy post-TIPS: current status and prospects in predictive assessment. Computational and Structural Biotechnology Journal. 2024 Jul; 24:493-506. Doi: 10.1016/j.csbj.2024.07.008
9. Ravindranath A, Srivastava A, Yacht SK, Poddar U, Sarma MS, Mathias A. Prevalence and Precipitants of Hepatic Encephalopathy in Hospitalized Children with Chronic Liver Disease. Journal of Clinical and Experimental Hepatology. 2024 Nov;14(6):101452. Doi: 10.1016/j.jceh.2024.101452
10. Waseem T, Latif SL, Chaudhary UC, Hanif FH. Effectiveness Of Oral Glutamine Challenge Test in Diagnosing Minimal Hepatic Encephalopathy in Liver Cirrhosis Patients. Journal of Akhtar Saeed Medical & Dental College. 2021 Jan;3(01). doi:10.1155/2013/547670
11. García-Martínez R, Diaz-Ruiz R, Ponceau M. Management of hepatic encephalopathy associated with advanced liver disease. Clinical Drug Investigation. 2022 Jun;42(Suppl 1):5-13. Doi: 10.1007/s40261-022-01146-6
12. Rehman S, Fatima QU, Rehman S, Sami Z, Ali H, Sadiqi I. Comparison of current and emerging strategies for treating hepatic encephalopathy. The Professional Medical Journal. 2021 Nov;28(12):1705-10. doi:10.29309/tam/2021.28.12.6644
13. Long L, Li H, Deng G, Wang X, Lu S, Li B et al. Impact of hepatic encephalopathy on clinical characteristics and adverse outcomes in prospective and multicenter cohorts of patients with acute-on-chronic liver diseases. Frontiers in Medicine. 2021 Aug; 8:709884. Doi: 10.3389/fmed.2021.709884
14. Duah A, Nkansah AA, Okine R, Duah F. Prevalence and Precipitating Factors of Hepatic Encephalopathy in Patients with Liver Cirrhosis and Ascites Admitted at Korle Bu Teaching Hospital in Ghana. Postgraduate Medical Journal of Ghana. 2021 Jul;10(1):31-6. doi:10.60014/pmjg.v10i1.248
15. Lim CG, Lee HJ. Pattern Clustering of Symmetric Regional Cerebral Edema on Brain MRI in Patients with Hepatic Encephalopathy. Journal of the Korean Society of Radiology. 2024 Mar;85(2):381. Doi: 10.3348/jksr.2023.0012
16. Belafonte D, Gioia S, Facciolo J, Riggio O, Radula L, Nardelli S. Old and new precipitants in hepatic encephalopathy: A new look at a field in continuous evolution. Journal of Clinical Medicine. 2023 Feb;12(3):1187.doi: 10.3390/jcm12031187
17. Zhu L, Zhang W, Chen L, Ren Y, Cao Y, Sun T et al. Brain gray matter alterations in hepatic encephalopathy: A voxel-based meta-analysis of whole-brain studies. Frontiers in human neuroscience. 2022 Apr; 16:838666. Doi: 10.3389/fnhum.2022.838666
18. Khan MS, Khan FU, Sohail M, Fahim M, Akhter S, Shahid M et al. Frequency of Upper Gastrointestinal Bleeding as Precipitant of Hepatic Encephalopathy among Patients with Liver Cirrhosis. Pakistan Journal of Medical & Health Sciences. 2022 Oct;16(08): 710-.doi:10.53350/pjmhs22168710
19. Triantafyllou K, Kolackies P, Gralen IM, Oakland K, Manes G, Radaelli F et al. Diagnosis and management of acute lower gastrointestinal bleeding: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2021 Aug;53(08):850-68. Doi: 10.1055/a-1496-8969
20. Khobragade H, Manohar T, Athawale A. Precipitating Factors and Clinic-Endoscopic Study of Patients with Hepatic Encephalopathy Type C. Journal of Contemporary Medicine. 2022 Jul;12(4):559-64. doi:10.61919/jhrr.v4i1.443
21. Sohail R, Hassan IH, Rukh M, Saqib M, Iftikhar M, Mumtaz H. Assessing Thrombocytopenia and Chronic Liver Disease in Southeast Asia: A Multicentric Cross-Sectional Study. Cures. 2023 Aug;15(8). Doi: 10.7759/cureus.43356
22. Jamal Inia M, Lonardo A, Neunkirchen R. Sex and gender differences in liver fibrosis: path mechanisms and clinical outcomes. Fibrosis. 2024 Oct;2(4):10006. doi:10.70322/fibrosis.2024.10006
23. Tapper EB, Saleh ZM, Nikirk S, Bajaj J, Chen X, Lok AS. Medically Tailored Meals for Patients with Cirrhosis and Hepatic Encephalopathy: The BRAINFOOD Proof-of-concept Trial. Journal of Clinical and Experimental Hepatology. 2024 Nov;14(6):101439. Doi: 10.1016/j.jceh.2024.101439
24. Huang DQ, Perrault NA, Tacke F, Gluud LL, Arrese M, Buginese E et al. Global epidemiology of cirrhosis—aetiology, trends and predictions. Nature reviews Gastroenterology & hepatology. 2023 Jun;20(6):388-98. Doi: 10.1038/s41575-023-00759-2
25. Montagnese S, Raito PE, Romero-Gómez M, Larsen FS, Shawcross DL, Thabit D et al. EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. Journal of hepatology. 2022 Sep;77(3):807-24. Doi: 10.1016/j.jhep.2022.06.001
26. Thabit D, Bouzid C, Meunier L, Haas M, Weiss N, Louvet A et al. Diagnosis and management of hepatic encephalopathy: The French recommendations. Liver International. 2023 Apr;43(4):750-62. Doi: 10.1111/liv.15510

27. Nardelli S, Gioia S, Facciolo J, Riggio O, Radula L. Hepatic encephalopathy–recent advances in treatment and diagnosis. Expert Review of Gastroenterology & Hepatology. 2023 Mar;17(3):225-35. Doi: 10.1080/17474124.2023.2183386