INTERNATIONAL JOURNAL OF ADVANCE RESEARCH, IDEAS AND INNOVATIONS IN TECHNOLOGY

ISSN: 2454-132X
Impact Factor: 6.078
(Volume 11, Issue 3 - V11I3-1363)
Available online at: https://www.ijariit.com

Regional Insights and Proposed Algorithm for Early Diagnosis and Management of Hepatic Encephalopathy

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ABSTRACT

Hepatic encephalopathy (HE) is a significant neuropsychiatric syndrome linked to liver dysfunction, presenting as either minimal hepatic encephalopathy (MHE) or overt hepatic encephalopathy (OHE). This review is based on focused group discussions of various experts across India, followed by guidance statements based on analysis of published literature, and designing a set of comprehensive algorithms to encourage early detection, intervention, diagnosis, and management of HE, as well as improve patient outcomes. The experts recommended using tests like the Psychometric Hepatic Encephalopathy Score (PHES) and Critical Flicker Frequency (CFF) reliable tool for diagnosing MHE, highlighting the need for specialized neuropsychological testing. In addition, the experts discussed the role of lactulose and rifaximin in reducing HE recurrence, and the potential benefits of probiotics, prebiotics, and symbiotics. Furthermore, the experts emphasized the importance of nutritional management, particularly intake of protein and branched-chain amino acids (BCAA) in the overall HE management. Liver transplantation may be considered in refractory cases. Regular follow-ups are crucial to monitor and adjust treatment strategies. By incorporating expert opinions and evidence-based practices into the designing of algorithms, the review aims to facilitate accurate and timely diagnosis, prompt intervention, and tailored treatment strategies, thereby reducing the variability in patient care, thus enhancing the quality of life for patients with HE.

Keywords: *Cirrhosis, minimal hepatic encephalopathy, overt hepatic encephalopathy, PHES, lactulose*

1. INTRODUCTION

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome associated with liver dysfunction, manifesting in two primary forms: early-stage HE i.e., minimal hepatic encephalopathy (MHE) or covert HE, and overt hepatic encephalopathy (OHE).[1,2] MHE is characterized by subclinical cognitive impairment with a significant effect on the quality of life and daily functioning that often goes unnoticed.[2,3] In contrast, OHE presents with clinical symptoms.[1,2] The pathogenesis of HE involves complex interactions between the liver-muscle-brain axis (Figure -1), particularly the accumulation of neurotoxins like ammonia that leads to neuroinflammation, altered neurotransmission, and oxidative stress, disrupting normal brain function.[2-4]

Early detection is vital as MHE can significantly impair cognitive function, contributing to accidents and decreased work productivity, impacting daily functioning and quality of life. Current diagnostic tools for MHE are often complex and not routinely used in clinical practice, leading to missed or delayed diagnosis.[2,3] This gap in diagnostic capability hinders timely intervention and treatment, emphasising the need for more accessible and accurate diagnostic criteria and tools.

Management of HE involves addressing precipitating factors, reducing ammonia levels, and preventing recurrence.[1,5] However, many patients continue to experience recurrent episodes or do not fully recover cognitive functions. This highlights a critical gap in effective long-term HE management strategies. In India, these challenges are exacerbated by limited resources and access to specialised care, underscoring the need for improved diagnostic criteria and management strategies tailored to local healthcare settings.

This review addresses the critical need for a consensus on developing an algorithm for diagnosing and managing MHE and OHE, specifically from the perspective of the Indian healthcare setup. The algorithm development process involved in-person focus group discussions (FGD) among expert gastroenterologists from across India, who collaboratively contributed to the algorithms based on available literature and their clinical experience. Creating a comprehensive framework would empower healthcare professionals with the tools to provide personalised and efficient care, ultimately optimising the healthcare delivery system for HE in India.

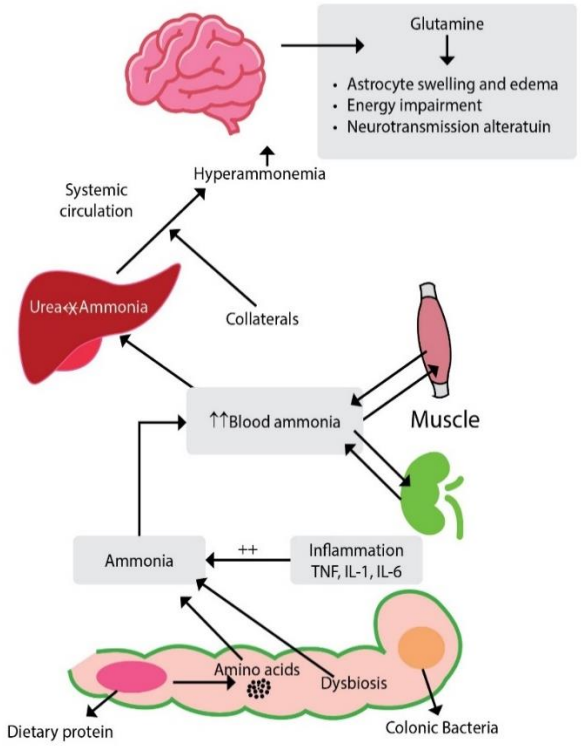

Figure -1: Pathogenesis of hepatic encephalopathy involving the liver-muscle-brain axis[2]

Physiologically, ammonia is released by the gut and microbiota. In healthy individuals, hepatocytes convert ammonia to urea, which is excreted through the kidneys (75%) and the intestine (around 25%). In liver cirrhosis, impaired ammonia extraction by the liver increases arterial ammonia levels, resulting in ammonia disposition in other tissues. In this case, the brain and muscles uptake and metabolize ammonia through glutamine synthetase, which converts ammonia and glutamate to osmotically active glutamine, leading to intracellular swelling and oedema.

2. EPIDEMIOLOGY

Epidemiological data indicate that HE is highly prevalent among patients with liver cirrhosis. Evidence suggests, 62.4% of cirrhotic patients exhibit subclinical HE, with 22.5% of these cases progressing to OHE within 6 months.[6] MHE is observed in 59.7% of cirrhotic individuals, underscoring the widespread occurrence of cognitive impairments in this population.[7] In those with HE, 60.19% experience new onset, while 39.81% face recurrent episodes.[8] Additionally, 32.9% of patients with non-cirrhotic portal hypertension also present with MHE.[9] The unique epidemiological factors in India, including a high prevalence of liver diseases due to hepatitis B, hepatitis C, and alcohol consumption, further complicate the HE burden.[8] The complexity of HE pathogenesis and clinical presentation demands robust clinical studies, which are currently insufficient in India.[1,10]

2.1 Insights from the focus group discussions:

The advisory board noted that the prevalence of HE ranges from 10-50% in patients who have undergone transjugular intrahepatic portosystemic shunt (TIPS) and increases to 16-21% in individuals with decompensated cirrhosis.

Limited awareness and deficiency of region-specific research make it difficult to address the unique epidemiological and clinical aspects of HE in the Indian population.

3. PRECIPITATING FACTORS

Referrals to specialists should focus on recognising early signs of liver disorders. Sethuraman *et al.* highlighted that among 103 patients, 88.35% of HE cases were due to alcohol, 4.85% to hepatitis B, and smaller percentages due to other causes such as hepatitis C. The distribution of HE severity was 3.88% for Grade I, 36.89% for Grade II, 39.81% for Grade III, and 19.42% for Grade IV. The mortality rate was 17.48%, with higher mortality associated with Grade IV HE. The precipitating factors for HE were predominantly dehydration (78.64%), infections (56.57%), and diuretics use (46.6%). Other significant factors included hypokalaemia (35.3%), constipation (33%), and gastrointestinal bleeding (30%). These factors exacerbate the accumulation of neurotoxins, such as ammonia, leading to the neuropsychiatric manifestations of HE.[8]

Plasma ammonia levels: Ammonia plays a pivotal role in the HE onset. Ammonia accumulation in brain disrupts neurotransmission and induces astrocyte swelling, leading to brain oedema and altered mental status.[8,11,12] In patients with delirium or encephalopathy and liver disease, a normal plasma ammonia level may question the diagnosis of HE. In addition, imaging techniques, such as computed tomography (CT) or Magnetic Resonance Imaging (MRI) scans, should be performed in case of diagnostic uncertainty or treatment failure.[10]

Constipation: Constipation is another critical precipitating factor for HE.[11,12] It increases the production and absorption of ammonia from the gut. In cirrhotic patients with constipation, the prolonged intestinal transit time increases bacterial degradation of nitrogenous substances. It results in higher ammonia levels, which aggravate HE symptoms.[11] Evidence suggests that chronic constipation may lead to gut dysbiosis, which is characterised by gut microbiota alterations with a parallel increase in potentially pathogenic microorganisms.[13] These may influence innate and adaptive immunity, resulting in systemic inflammation.[14]

Gut dysbiosis: Gut dysbiosis has recently been recognised as a critical factor in HE.[11,12] Dysbiosis leads to an increase in the production of ammonia and other neurotoxic substances by pathogenic bacteria. This imbalance disrupts the gut barrier, resulting in increased translocation of bacteria and their toxins into the bloodstream, which triggers systemic inflammation and worsens HE.[12]

Systemic infections: Infections, including spontaneous bacterial peritonitis, urinary tract infections, and respiratory infections, are significant triggers for HE episodes.[8] These infections induce systemic inflammation and increase the permeability of the blood-brain barrier, which facilitates the entry of neurotoxins into the brain. The inflammatory response to infection also leads to the production of cytokines that can further impair cerebral function, exacerbating the neuropsychiatric symptoms of HE.[8,11,12]

3.1 Insights from experts:

Clinicians should evaluate the precipitating factors for HE that increase the MHE risk. These factors include chronic liver diseases, including alcoholic liver disease, non-alcoholic steatohepatitis, viral hepatitis, along with non-cirrhotic portal hypertension, GI bleeding, diabetes, acute kidney injury, diuretic use, and constipation. They noted that TIPS could precipitate HE.

Further evaluation is suggested in patients who have experienced the following events within the last year: a history of road traffic accidents, unprovoked falls, increased fatigue, and decreased attention span. A checklist has been provided to assess the likelihood of possible MHE (Figure -2). If any of the conditions persist, caregivers should be educated on how to monitor MHE symptoms, and the patient should undergo regular screening.

The experts highlighted that, although often overlooked, it is essential to specify whether HE is precipitated, spontaneous, or recurrent, along with identifying the precipitant. The precipitant is the primary target for treatment, which can facilitate patient recovery within 3 to 4 days.

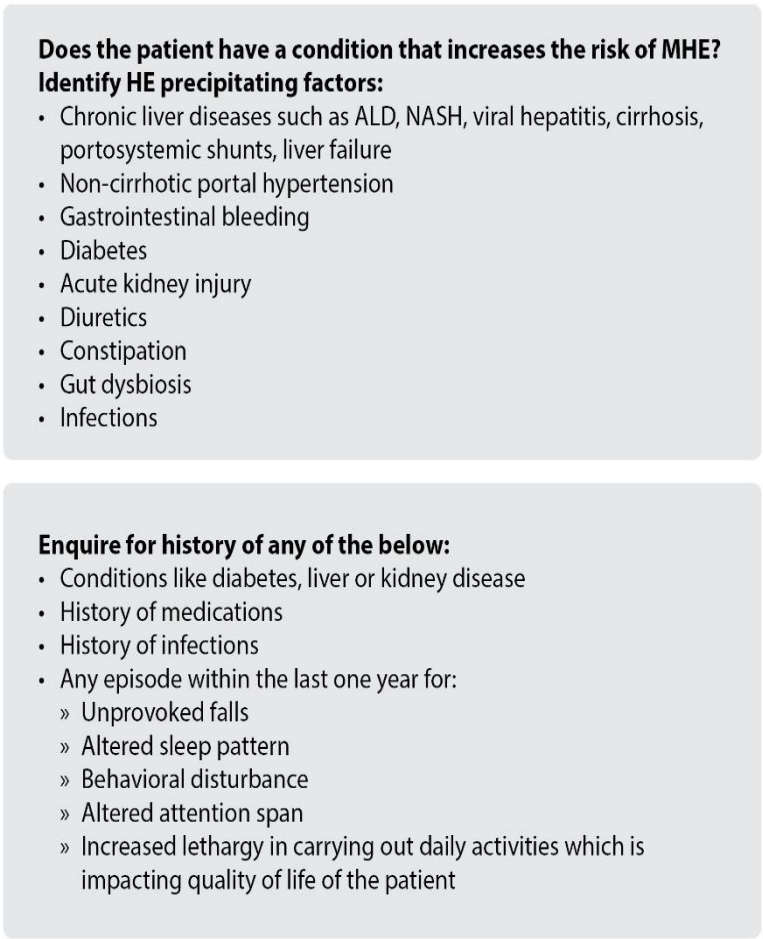

Figure -2: Checklist for possible MHE

4. DIAGNOSIS

West Haven Criteria (WHC) is the gold standard for HE diagnosis. It categorises HE based on the severity of clinical manifestations, ranging from minimal (subclinical alterations) to Grade IV, and assesses the continuum of cognitive and motor impairments (Table-1).[15]

Table-1: West Haven Criteria (WHC) for HE and its clinical description.[8]

WHC category	ISHEN	Clinical Presentation
Minimal	Covert	• Psychometric/neuropsychological changes in tests or neurophysiological changes. • No clinical evidence of mental change.
Grade I		• Trivial lack of awareness • Euphoria/anxiety • Shortened attention span • Impaired addition/subtraction
Grade II	Overt	• Lethargy/apathy • Disorientation to time • Obvious personality change • Inappropriate behaviour
Grade III		• Somnolence to semi-stupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behaviour
Grade IV		Coma
ISHEN: International Society for Hepatic Encephalopathy and Nitrogen Metabolism		

4.1 Tests for diagnosis of MHE:

Psychometric tests: Psychometric tests play a crucial role in diagnosing MHE. These tests jointly assess various cognitive domains, such as psychomotor speed, visual-spatial orientation, and attention, providing a comprehensive evaluation of cognitive function.[3] The Psychometric Hepatic Encephalopathy Score (PHES) is one of the most used tools and is considered the gold standard for diagnosing MHE.[3,15-17] It comprises five paper-pencil tests, including the Digit Symbol Test, Number Connection Tests A and B, Line Tracing Test, and Serial Dotting Test.[15,16] These tests collectively last for approximately 15 minutes, and a score less than -4 indicates the presence of MHE.[3,16]

Stroop test has gained validation against PHES, providing a quick and reliable assessment tool for clinical settings.[1,16,17] The SCAN test, measuring speed and accuracy in digit recognition tasks, and the Continuous Reaction Time (CRT) test, assessing motor reaction to auditory stimuli, were highlighted for their insights into cognitive function.[17]

Neurophysiological tests: Critical Flicker Frequency (CFF) test and Electroencephalography (EEG) have been recommended for detecting cortical brain activity changes.[1,16,17] CFF is a method to assess cognitive functions by evaluating the maximum speed of flickering light that can be perceived by the visual system. It is objective, simple, quick, and is not affected by factors such as a level of education or language.[1,16] CFF has shown statistically significant efficacy in identifying subclinical HE (SHE) and exhibits a strong correlation with PHES in distinguishing healthy individuals from those with HE.[18] EEG is a test that identifies variations in cortical brain activity throughout the spectrum of HE. EEG can be evaluated without patient co-operation and is not influenced by a learning effect.[1,17]

Neuroimaging: CT and MRI scans have a role in evaluating metabolic encephalopathies, which could provide pathophysiological insights into HE.[16,17,19] A CT scan is valuable for assessing cerebrospinal fluid and ventricular volumes, providing critical information about cerebral oedema in severe HE cases.[19] The advisory board concurred that a brain CT scan is primarily performed to exclude other pathologies rather than to diagnose HE. This ensures that other potential causes of encephalopathy are not overlooked, particularly in patients with clinically suspected encephalopathy and normal blood ammonia levels.[1,16,17,19]

Laboratory tests: These help to identify underlying liver dysfunction and precipitating factors. Serum ammonia levels are commonly measured. However, ammonia levels do not consistently correlate with HE severity.[16,19,20]

Comprehensive liver function tests, including measurements of bilirubin, albumin, and prothrombin time, provide insights into the liver's synthetic capacity and overall function. Additionally, blood tests are critical to rule out infections, electrolyte imbalances, and renal dysfunction, as these conditions can exacerbate HE.[19,20] Recent research has also explored the role of inflammatory markers and gut microbiota profiles in the pathogenesis of HE, suggesting potential new biomarkers for diagnosis and monitoring.[12]

Assessment for severity of liver disease: The BABS (Bilirubin, Albumin, nonselective Beta-blocker, Statin) score and MASQ-HE (MELD-Na-Activity-Chair Stands-Quality of Life) score are significant tools for predicting the transition from MHE to OHE. The BABS score utilizes bilirubin, albumin levels, and the use of nonselective beta-blockers and statins to stratify patients into three risk categories.

Patients with a low-risk score (≤10) have a 27% risk of developing OHE over five years, whereas those with intermediate (11-20) and high-risk (≥21) scores have a 49% risk.[21] One benefit of the BABS score compared to the PHES or CFF is that it was specifically developed to predict OHE.[22]

Conversely, the MASQ-HE score, developed to predict 12-month OHE risk, combines the Model of End-Stage Liver Disease Sodium (MELD-Na) score with assessments of activity, frailty, and quality of life. This score demonstrated an area under the curve of 0.82 for predicting OHE development and 0.92 for HE-associated hospitalization.[21,22] These scores are essential in clinical practice for early identification and management of patients at risk for OHE, aiding in proactive patient counselling and potential interventions to mitigate HE progression.

The Child-Pugh classification is a vital tool for assessing the prognosis of chronic liver disease and cirrhosis by evaluating encephalopathy, ascites, bilirubin, albumin, and prothrombin time (INR). Scores for each parameter range from 1 to 3, categorising patients into Class A (5-6 points), Class B (7-9 points), and Class C (≥10 points), with Class A indicating the best prognosis and Class C the worst.[6,8] Table-2 summarises the various pros and cons of the diagnostic tests of HE.

Table-2: Pros and cons of HE diagnostic tests[1,8,9,15-18,20,21]

Test Category	Pros	Cons
Psychometric Tests	• Sensitive and specific for early cognitive impairment (Eg, PHES) • Easy to administer • Validated across different populations	• Time-consuming in nature • Affected by education level, language, and age • Insensitive to early changes
Neurophysiological Tests	• Less influenced by education or language • Can detect MHE and predict OHE	• Require specialised equipment and trained operators • May not be readily available in routine settings
Neuroimaging	• Useful to rule out alternative causes of encephalopathy, including haemorrhage, masses, or intracranial lesions • Helps differentiate MHE from other neurologic disorders	• High cost and limited availability • Not specific for MHE in early stages • Not routinely used for HE detection
Laboratory Tests	• Widely available • Helpful in supporting diagnosis and understanding pathophysiology	• Poor correlation with clinical symptoms of MHE • Non-specific; ammonia may be normal in MHE • May be affected by chronic inflammatory conditions

4.2 Insights from experts:

Combining the WHC with the Mini-Mental Status Test (MMST)/ Mini-Mental State Examination (MMSE) can enhance its reliability. MMST is a tool comprising of 11 questions that systematically and thoroughly assesses mental status. It measures five areas of cognitive function: language, recall, attention and calculation, orientation, and registration (Supplementary I). An MMST score of 24-30 is considered normal, while scores below 24 may indicate cognitive impairment. For HE, a score of 25 or less suggests the presence of cognitive deficits, warranting further evaluation and management (Figure -3).

PHES is accessible, sensitive, and cost-effective, with high agreement among experts regarding its use. The advisory board reported that PHES is an ideal and reliable tool for diagnosing MHE and predicting survival outcomes. However, it takes roughly 15 minutes and is not practical for professionals to give 15 minutes to each patient. Also, these are not random tests, but normative tests. Given that the PHES is time-consuming, influenced by patient literacy and education levels, there is a clear need for a faster, objective, and reproducible diagnostic test.

Physicians should promptly repeat blood counts whenever a patient with new-onset ascites experiences any changes, signs of decompensation, or requires hospitalisation.

The importance of considering non-hepatic causes of hyperammonaemia and the limited correlation between ammonia levels and HE severity was also discussed and agreed upon. Serum ammonia, with a cutoff of 150-200 mmol/L, may be useful if the HE diagnosis is uncertain.

The experts emphasised that MRI is not routinely employed for diagnosing HE due to the lack of consensus on its usage.

The discussion also highlighted that positron emission tomography offers valuable insights into the pathophysiological changes leading to altered neuropsychiatric examinations.

It was emphasised that BABS and MASQ-HE are the predictors of OHE onset. Low albumin and high bilirubin levels indicate severe liver dysfunction. The use of nonselective beta-blockers relates to portal hypertension, while statin usage reflects underlying comorbidities.

The experts noted that while numerous studies have investigated elevated inflammatory markers, oral glutamine challenge tests and ammonia levels (1.5 times higher than normal) are indicators for developing OHE, however, such research remains relatively uncommon.

The experts emphasized that spontaneous HE cases typically require longer hospital stays compared to precipitated ones. Many patients who are admitted once tend to be readmitted within 1 to 3 months, classifying their condition as recurrent encephalopathy. Most patients with Child-Turcotte-Pugh C who are referred for transplantation usually suffer from some form of persistent HE. Therefore, it was agreed that the grade, precipitant, and type of HE should be documented.

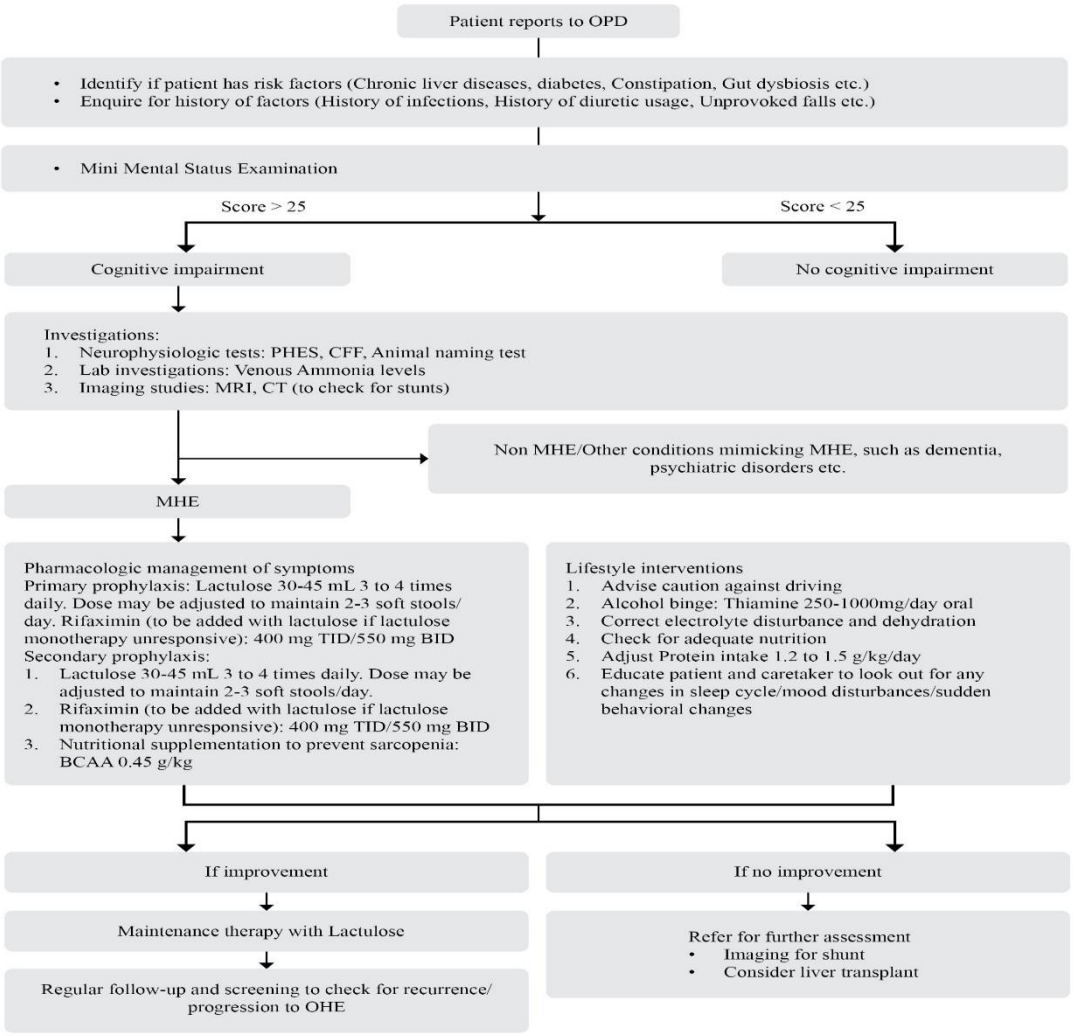

Figure -3: Algorithm for MHE

5. MANAGEMENT

HE management involves a multifaceted approach that targets the underlying precipitating factors, reduces ammonia production, prevents HE recurrence, and improves patient outcomes.[1,5,17,23]

Precipitating factors: The initial step in managing HE is to identify and treat precipitating factors such as infections, gastrointestinal bleeding, electrolyte imbalances, and constipation.[23,24] For instance, gastrointestinal bleeding leads to elevated blood ammonia levels and necessitates the use of endoscopic interventions and haemostatic agents to control the source of bleeding.[11,24]

Prebiotics, probiotics, and synbiotics: Evidence from recent studies supports the use of probiotics, prebiotics, and synbiotics in managing HE.[12,25] Prebiotics have emerged as a promising adjunctive treatment for HE due to their ability to modulate gut microbiota and reduce ammonia production.[11,12] A meta-analysis demonstrated that these interventions significantly reduced the pooled relative risk of no improvement of MHE (RR 0.40, $p < 0.001$), indicating a substantial benefit. Subgroup analyses revealed that lactulose, a prebiotic, had the most significant effect on RR of no improvement of MHE (RR 0.34, $p < 0.0001$). Probiotics and synbiotics also showed significant benefits with RR of 0.41 ($p < 0.0001$) and 0.51 ($p = 0.004$), respectively. These findings highlight the potential of gut microbiota modulation in improving outcomes for MHE patients.[25]

Lactulose: Lactulose remains the cornerstone of HE treatment due to its ability to lower ammonia levels by acidifying the gut and promoting ammonium excretion.[1,5,10] It decreases the intestinal production and absorption of ammonia, helping to detoxify the colon and lower systemic ammonia levels. It is indicated for the prevention and treatment of portal-systemic encephalopathy, including all stages from hepatic pre-coma to coma.[26] Studies have shown that lactulose reduces the recurrence of HE episodes and improves cognitive function in patients with cirrhosis. A meta-analysis reported that lactulose was the only agent effective in reducing ammonia, reversing minimal HE, preventing overt HE, and improving quality of life, with tolerable adverse effects in patients with

cirrhosis.[27] In addition, a Cochrane review analysing 38 clinical trials demonstrated that lactulose reduces the risk of overt HE episodes (RR 0.58, 95% CI 0.50–0.69). An open-label, single-centre randomised study reported that treatment with lactulose significantly reduced HE incidence in patients with gastrointestinal bleeding ($p < 0.03$), although it had no significant impact on survival. Similarly, another single-centre open-label randomised study reported a significant reduction in HE incidence with lactulose treatment ($p < 0.02$).[10]

In MHE, lactulose is recommended for both primary and secondary prophylaxis at a dose of 30–45 mL, administered 2-3 times daily. The dose should be adjusted to achieve and maintain 2–3 soft stools per day. In OHE, oral lactulose therapy is initiated with 20 g (30 mL) every two hours until clinical improvement is observed, characterized by achieving 2–3 soft stools daily or the development of acidic stools. In patients who are comatose or unable to tolerate oral intake, rectal administration of lactulose—300 mL diluted in 1000 mL of water—every two hours is recommended until recovery. Maintenance therapy following stabilization involves continuing oral lactulose at a dose of 30–45 mL daily, titrated to maintain regular bowel movements and prevent recurrence of encephalopathy.

Antibiotics: Rifaximin, a non-absorbable antibiotic, is beneficial as an adjunct to lactulose therapy. Clinical trials have demonstrated that rifaximin, when used in combination with lactulose, significantly reduces HE recurrence rates and hospitalisations.[1,23,24,28] Another randomised, double-blind, placebo-controlled trial found that rifaximin 550 mg twice daily effectively maintained remission from recurrent HE and reduced HE-related hospitalisations over six months. Patients receiving rifaximin had a significantly lower risk of breakthrough HE episodes (22.1% vs. 45.9%; $p<0.001$) and hospitalisation (13.6% vs. 22.6%; $p=0.01$) compared to placebo. More than 90% of patients received concomitant lactulose therapy. These results support rifaximin as an effective therapy for preventing HE recurrence and associated hospitalisations.[28] Similarly, a large double-blind, placebo-controlled RCT supports the use of rifaximin in patients with cirrhosis for the prevention of post-TIPS HE. Rifaximin 600 mg twice daily significantly reduced the incidence of overt HE over the subsequent 168 days. Rifaximin therapy was initiated 14 days before TIPS placement and continued for approximately six months. However, the potential long-term benefits of rifaximin beyond six months post-TIPS remain to be elucidated.[10]

Nutrition: Protein intake, which was previously restricted, is now encouraged to maintain muscle mass and prevent malnutrition.[1,10] Recent guidelines recommend a daily protein intake of 1.2-1.5 g/kg body weight in patients with HE. Vegetable proteins or branched-chain amino acids (BCAAs) supplements may be considered in patients who experience worsening of symptoms or are intolerant to dietary proteins.[1,20] Patients with hyperammonaemia frequently experience amino acid deficiencies, particularly a depletion of BCAAs.[17,20] Decreased BCAA plasma levels result in a reduced BCAA/aromatic amino acids (AAA) ratio (Fisher ratio), which is negatively correlated with HE severity. BCAAs compete with AAAs at the blood-brain barrier, and their deficiency contributes to disrupted neurotransmission. Additionally, skeletal muscle serves as an extrahepatic site for ammonia detoxification, a process dependent on BCAA availability. However, cirrhosis-associated muscle wasting impairs this compensatory mechanism. BCAA supplementation has been shown to enhance ammonia clearance, modulate neurotransmitter balance, and potentially mitigate both HE and sarcopenia.[29]

Multiple trials have examined the impact of oral BCAA supplementation, demonstrating beneficial effects on HE.[20,23,29] Oral BCAA supplementation has been shown to induce a positive nitrogen balance, improve muscle protein synthesis and muscle mass, improve event-free survival, and enhance MHE outcomes.[24,29] However, no definitive benefit on mortality, quality of life, or nutritional parameters have been established.[20,23]

Endogenous amino acid: Recent research examines the role of L-ornithine and L-aspartate (LOLA) in managing HE, highlighting its effects on plasma ammonia levels and HE symptoms.[25] LOLA treatment shows significant reductions in serum ammonia and improvements in mental state and psychometric scores.[5,30] The combination of LOLA with rifaximin and lactulose has proven to be more effective in improving HE grades compared to using lactulose or rifaximin alone. Additionally, acetyl-L-carnitine has shown promising action in reducing ammonia levels, however, its use remains experimental.[16]

Liver transplantation: For patients with recurrent or persistent HE unresponsive to medical therapy, liver transplantation offers a definitive cure by addressing the underlying liver dysfunction.[1,10,23] Data from the United Network for Organ Sharing (UNOS) registry indicates that post-transplant survival rates are significantly improved, with one-year survival rates exceeding 65% for patients undergoing transplantation for HE.[31] Recurrent or persistent HE is often driven by spontaneous portosystemic shunting, and identifying and obliterating dominant shunts should be considered in patients with a MELD score <11. Post-TIPS HE can be managed through shunt reduction or closure. If no shunts are identified, occlusion is ineffective, or liver function is severely impaired, liver transplantation remains the definitive treatment.[10] Determining the optimal timing for liver transplantation in HE can be challenging, as the MELD score, a key criterion for organ allocation, does not account for HE severity. A pragmatic approach is to consider transplantation when a patient has:

- Experienced an index complication, including HE, with a MELD score >15.
- A history of recurrent hospitalizations for overt HE.[10]

Patients with chronic persistent HE and mild hepatic insufficiency may also be considered for transplantation if all other treatments have failed. However, careful pre-transplant evaluation is necessary, as HE symptoms may not always resolve immediately post-transplant. Additionally, meticulous attention should be given to closing all shunts during the transplantation procedure to optimize outcomes.[10]

5.1 Insights from experts:

Variations were found in the real-world administration of lactulose, thus recommending training for nurses to ensure its proper use. It is imperative to recognise the benefits of lactulose enemas as an alternative administration route for patients unable to tolerate oral medications or experiencing acute HE episodes. One panellist suggested administering lactulose enemas every 2 hours rather than every hour.

The experts advised adding Rifaximin to lactulose for secondary prophylaxis following one or more episodes of overt HE within six months of a prior episode. One panellist mentioned that after administering lactulose and rifaximin for six months following an HE episode, it may be advisable to discontinue treatment and monitor the patient's condition.

Adequate BCAAs and α-ketoglutarate intake, along with nutrition and exercise, may help prevent HE. The FGD members also highlighted that optimal timing for initiating these interventions, potentially in the presymptomatic phase, is a key factor for improving outcomes in cirrhotic patients at risk of sarcopenia and HE.

It was recommended to consider liver transplantation for patients with recurrent or persistent HE. Those with overt HE grades 3 and 4, who are at risk of aspiration, may benefit from ICU admission. Decisions regarding ICU admission and liver transplantation should be based on clinical judgment and evaluated individually for each patient.

Before discharge, the patient's neurological status must be confirmed, distinguishing HE-related deficits from other conditions. Caregivers should be informed about potential changes in neurological status and medication needs. Precipitating factors must be recognised, and future management to be planned based on liver function improvement, portosystemic shunts, and infection prevention.

Post-discharge consultations should be scheduled to adjust treatment and prevent HE recurrence, with coordination ensured with family and primary care providers. Education on medication effects, adherence, early HE signs, and response actions is essential for patients and relatives.

Follow-ups are crucial in HE management as they help monitor the patient's response to treatment, detect early signs of recurrence, and adjust therapeutic strategies accordingly. Regular follow-ups ensure adherence to medications, lifestyle modifications, and the effectiveness of interventions, ultimately improving patient outcomes and reducing hospital readmissions.

The experts stressed that identifying MHE is crucial because it allows OHE prevention, which in turn helps avert a poor prognosis. The algorithms presented in Figure -3 and Figure -4 detail a systematic approach for diagnosing and managing MHE and OHE, respectively. These algorithms reflect the collective perspective of the FGD members.

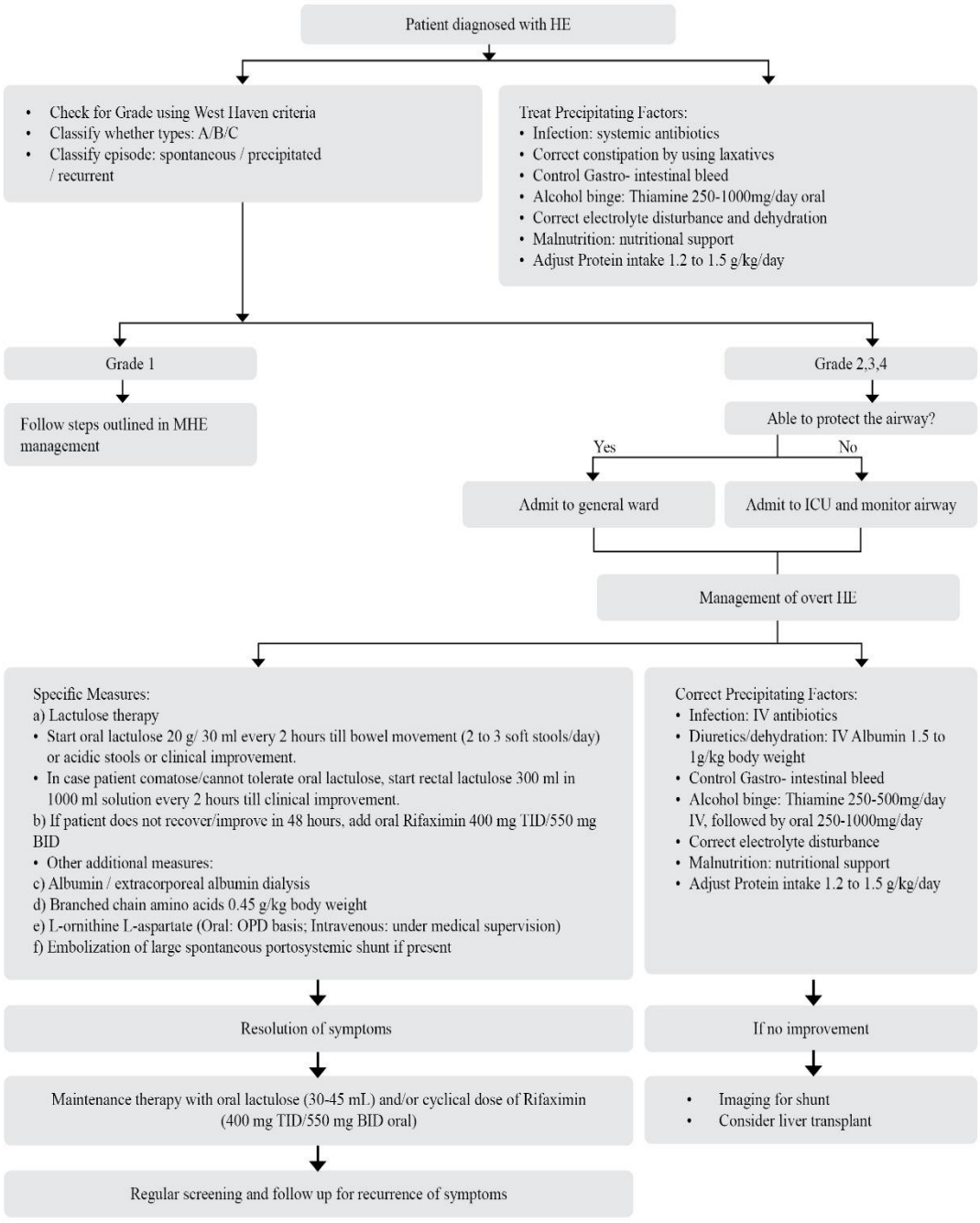

Figure -4: Algorithm for OHE

6. CONCLUSION

The development and implementation of standardized diagnostic and management algorithms for HE are essential in enhancing patient care and outcomes, particularly in resource-constrained settings like India. These algorithms provide a structured approach to early diagnosis and systematic management of both MHE and OHE, addressing the significant gaps identified in current clinical practice.

By incorporating expert opinions and evidence-based practices, these algorithms facilitate accurate and timely diagnosis, prompt intervention, and tailored treatment strategies, thereby reducing the variability in patient care and improving the quality of life for patients. Furthermore, these frameworks empower healthcare professionals to better manage the complexities of HE, ultimately leading to reduced recurrence rates and hospitalizations. Continued research and refinement of these algorithms will ensure they remain relevant and effective, promoting uniformity and excellence in the management of hepatic encephalopathy across diverse clinical settings.

7. ACKNOWLEDGEMENT

We acknowledge Medicca Press for providing editorial assistance.

REFERENCES

[1] Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice guideline by the American Association for the study of liver diseases and the European Association for the study of the liver. Hepatology. 2014;60(2):715-735.
[2] Shiha G, Mousa N. Minimal Hepatic Encephalopathy: Silent Tragedy [Internet]. Liver Disease and Surgery [Working Title]. IntechOpen; 2019. Accessed June, 2024. Available from: http://dx.doi.org/10.5772/intechopen.88231
[3] Faccioli J, Nardelli S, Gioia S, et al. Minimal hepatic encephalopathy affects daily life of cirrhotic patients: A viewpoint on clinical consequences and therapeutic opportunities. J Clin Med. 2022;11:7246.
[4] Guo Z, Yu Z, Hu K-Q. Overview on current management of hepatic encephalopathy. N A J Med Sci. 2016;9(2):59-65.
[5] Dhiman RK, Saraswat VA, Sharma BK, et al. Minimal hepatic encephalopathy: Consensus statement of a working party of the Indian National Association for Study of the Liver. J Gastroenterol Hepatol. 2010;25(6):1029-1041.
[6] Das A, Dhiman RK, Saraswat VA, et al. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. J Gastroenterol Hepatol. 2001;16:531-535.
[7] Rathi S, Chopra M, Chouduri G, et al. Prevalence of minimal hepatic encephalopathy in patients with liver cirrhosis: A cross-sectional, clinicoepidemiological, multicenter, nationwide study in India: The PREDICT study. J Clin Exp Hepatol. 2019;9(4):476-483.
[8] Sethuraman VK, Balasubramanian K. Clinical spectrum of precipitating factors of hepatic encephalopathy in cirrhosis of liver and its relation to prognosis in a tertiary care hospital – A retrospective study. Int J Contemp Med. 2019;4(2):B65-B70.
[9] Giri S, Singh A, Angadi S, et al. Prevalence of hepatic encephalopathy in patients with non-cirrhotic portal hypertension: A systematic review and meta-analysis. Indian J Gastroenterol. 2023;42:642650.
[10] European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. J Hepatol. 2022;77:807-824.
[11] Bellafante D, Gioia S, Faccioli J, et al. Old and new precipitants in hepatic encephalopathy: A new look at a field in continuous evolution. J Clin Med. 2023;12:1187.
[12] Bajaj JS. The role of microbiota in hepatic encephalopathy. Gut Microbes. 2014;5(3):397-403.
[13] Zhao Y, Yu YB. Intestinal microbiota and chronic constipation. Springerplus. 2016 Jul 19;5(1):1130.
[14] Pan R, Wang L, Xu X, Chen Y, Wang H, Wang G, et al. Crosstalk between the Gut Microbiome and Colonic Motility in Chronic Constipation: Potential Mechanisms and Microbiota Modulation. Nutrients. 2022 Sep 8;14(18):3704.
[15] Weissenborn K. Hepatic encephalopathy: Definition, clinical grading and diagnostic principles. Drugs. 2019;79(Suppl 1):S5-S9.
[16] Higuera-de-la-Tijera F, Velarde-Ruiz Velasco JA, Raña-Garibay RH, et al. Current vision on diagnosis and comprehensive care in hepatic encephalopathy. Rev Gastroenterol Méx. 2023;88:155-174.
[17] Vidal-Cevallos P, Chávez-Tapia NC, Uribe M. Current approaches to hepatic encephalopathy. Ann Hepatol. 2022;27:100757.
[18] Kircheis G, Wettstein M, Timmermann L, Schnitzler A, Häussinger D. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. Hepatology. 2002 Feb;35(2):357–66.
[19] Karanfilian BV, Cheung M, Dellatore P, et al. Laboratory abnormalities of hepatic encephalopathy. Clin Liver Dis. 2020;24(2):197-208.
[20] Mandiga P, Kommu S, Bollu PC. Hepatic Encephalopathy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Updated March 2024. Accessed July, 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430869/
[21] Redfield R, Latt N, Munoz SJ. Minimal hepatic encephalopathy. Clin Liver Dis. 2024;28:237-252.
[22] Gairing SJ, Schleicher EM, Galle PR, Labenz C. Prediction and prevention of the first episode of overt hepatic encephalopathy in patients with cirrhosis. Hepatol Commun. 2023;7(4):e0096.
[23] Rudler M, Weiss N, Bouzbib C, et al. Diagnosis and management of hepatic encephalopathy. Clin Liver Dis. 2021;25:393–417.
[24] Rose CF, Amodio P, Bajaj JS, et al. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. J Hepatol. 2020;73:1526-1547.
[25] Shukla S, Shukla A, Mehboob S, Guha, S. Meta-analysis: the effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy. Aliment Pharmacol Ther. 2011;33:662-671.
[26] Mukherjee S, Patel P, John S. Lactulose. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Apr 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK536930/

[27] Dhiman RK, Thumburu KK, Verma N, Chopra M, Rathi S, Dutta U, et al. Comparative Efficacy of Treatment Options for Minimal Hepatic Encephalopathy: A Systematic Review and Network Meta-Analysis. Clinical Gastroenterology and Hepatology. 2020 Apr 1;18(4):800-812.e25.
[28] Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010;362:1071-1081.
[29] Marrone G, Serra A, Miele L, et al. Branched chain amino acids in hepatic encephalopathy and sarcopenia in liver cirrhosis: Evidence and uncertainties. World J Gastroenterol. 2023 May 21;29(19):2905–15.
[30] Canbay A, Götze O, Kucukoglu O, et al. L-Ornithine-L-Aspartate (LOLA) normalizes metabolic parameters in models of steatosis, insulin resistance and metabolic syndrome. Pharmaceutics. 2024;16:506.
[31] Yoon JU, Yoo YM, Byeon GJ, et al. The impact of pretransplant hepatic encephalopathy, model for end-stage liver disease (MELD) scale on long-term survival following deceased donor liver transplantation: a retrospective study. Ann Palliat Med. 2021;10(5):5171-5180.