REVIEW

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Glymphatic Dysfunction in Hepatic Encephalopathy: A Novel Pathogenetic Pathway and Potential Target for New Therapeutic Opportunities

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ABSTRACT

Hepatic encephalopathy (HE) is a common complication of decompensated liver cirrhosis and acute-on-chronic liver failure. It encompasses a range of symptoms, from minimal cognitive impairments to severe personality changes and even coma. Liver dysfunction, coupled with the development of portosystemic shunting (PSS), leads to the accumulation of toxic substances in the brain, adversely affecting its function. Common precipitating factors for HE include variceal bleeding, infections, and electrolyte imbalances. However, other mechanisms likely contribute to the onset of HE, as some patients experience episodes without identifiable predisposing factors. These patients may remain in a chronic state of latent HE or have increasingly frequent episodes of HE. One potential contributing factor to HE is dysfunction of the glymphatic system (GS), which clears metabolic waste from the brain. This review aims to highlight the mechanisms underlying GS dysfunction in individuals with liver cirrhosis and explore how it may relate to the development of HE. Additionally, it will provide information on therapeutic interventions that target glymphatic dysfunction, potentially offering new treatment options for HE in the future.

Key words: hepatic encephalopathy – glymphatic system – cirrhosis – portal hypertension.

Abbreviations: ANS: autonomic nervous system; AQP4: aquaporin-4; AQP4-KO: AQP4-knockout; BBB: blood–brain barrier; BDL: bile duct-ligated; CNS: central nervous system; CSF: cerebrospinal fluid; DTI-ALPS: diffusion tensor imaging analysis along the perivascular space; FXR: farnesoid X receptor; GABA: gamma-aminobutyric acid; GS: glymphatic system; HE: hepatic encephalopathy; ISF: interstitial fluid; MASLD: metabolic-associated steatotic liver disease; MHE: minimal hepatic encephalopathy; MRI: magnetic resonance imaging; mtROS: mitochondrial reactive oxygen species; PEA: phenylethylamine; PHES: psychometric HE score; PPS: portosystemic shunting; PVS: perivascular space; RCT: randomized controlled trial; *R. gnavus: Ruminococcus gnavus*; S1P2R: sphingosine-1 phosphate receptor-2; SNS: sympathetic nervous system; Snta: syntrophin; TGR5: Takeda-G coupled protein receptor 5; VNS: vagus nerve stimulation; VRS: Virchow-Robin spaces; WHC: West Haven Criteria.

INTRODUCTION

Hepatic encephalopathy (HE) is a serious complication that may occur in cases of severe acute or chronic liver failure and/or in the presence of portosystemic shunting (PSS) and is characterized by alterations in personality, as well as cognitive and motor dysfunction [1]. Even in its mildest form, HE significantly affects patients' quality of life, and unless the underlying liver disease is successfully treated, it is associated with a high risk of recurrence and poor survival [2]. Traditionally, three types of HE are distinguished by underlying cause and classified as follows: type A in acute liver failure; type B due to portosystemic shunts in the absence of intrinsic liver disease; and type C in patients with liver cirrhosis and PSS [3]. An additional classification is based on severity: minimal hepatic encephalopathy (MHE) and HE grades I-IV according to the West Haven Criteria (WHC). The WHC considers a broad spectrum of neurological disorders, ranging from mild neuropsychiatric disturbances, such as changes in attention or behavior, to lethargy or even coma. Minimal hepatic encephalopathy, on the other hand, has been recognized as a distinct entity characterized by abnormalities detected through specialized psychometric tests or neurophysiological assessments in the absence of overt clinical symptoms [4].

PATHOPHYSIOLOGY OF HEPATIC ENCEPHALOPATHY

The Role of the Gut-Liver–Brain Axis Failure

Hepatic encephalopathy occurs when liver failure or PSS disrupts brain function, causing a cascade of neurological disorders ranging from barely perceptible symptoms to coma [5]. It is now well established that the progression of HE is multifactorial and driven by gut–liver–brain axis failure [6]. The gut–liver–brain axis is a bidirectional communication network linking the gut microbiota, the liver, and the brain through metabolic, immune, and neurohormonal pathways [7]. Initially, metabolic products of intestinal bacteria, such as short-chain fatty acids, ammonia, and toxins, are transported via the portal circulation to the liver, thereby affecting its function [6, 8]. In addition, reduced intestinal motility and subsequent bacterial overgrowth, along with the increased intestinal permeability ("leaky gut") observed in cirrhosis and portal hypertension, lead to bacterial translocation through the systemic circulation. This results in activation of the immune system and the release of inflammatory mediators [9, 10], which, in turn, may disrupt the blood–brain barrier (BBB) [11]. Furthermore, intestinal bacterial overgrowth alters the production of neurotransmitters such as serotonin, gamma-aminobutyric acid (GABA), and dopamine in the gut, thereby affecting the balance of enteroendocrine and neuromuscular function, which can lead to mood disturbances, anxiety, and neurocognitive deficits [12, 13].

Neuro-glia-vascular Failure

In HE, a dysfunction in the neuroglial unit seems to be present, affecting nutrient delivery, blood flow to the brain, and the proper functioning of the BBB [14]. Studies have identified a strong correlation between changes in the intestinal microbiome and systemic inflammation, elevated ammonia levels (hyperammonemia), and, ultimately, dysfunction in neurons and astrocytes in patients with cirrhosis [15]. In the pathogenesis of HE, recent reviews have also implicated the glymphatic system, linking impaired glymphatic drainage to the buildup of toxic metabolic by-products and agents that contribute to worsening brain function [16]. Therefore, to comprehensively understand the pathophysiology of HE, factors such as hyperammonemia, systemic inflammation, circulatory dysfunction, and dysregulation of the glymphatic system should be examined as a whole, rather than individually.

Ammonia and Bile Acids

The primary mechanism underlying the pathophysiology of HE is cerebral edema caused by hyperammonemia. Liver damage impairs ammonia clearance from the bloodstream, leading to elevated plasma and brain ammonia levels. In the latter, the astrocytes play a crucial role in detoxifying excess ammonia by converting it into glutamine. However, the accumulation of glutamine within cells leads to cytotoxic edema and disrupts neurons' supporting functions [17].

While hyperammonemia has been extensively studied, recent literature has also identified a link between abnormal bile acid signaling and the development of HE. Specifically, in the context of an already compromised BBB, unconjugated and taurine-conjugated bile acids can cross the BBB and bind to neuronal receptors, such as the farnesoid X receptor (FXR), the Takeda-G coupled protein receptor 5 (TGR5), and the sphingosine-1 phosphate receptor-2 (S1P2R). This results in altered membrane excitability, promoting neurotoxicity [18]. The osmotic stress caused by glutamine accumulation, combined with the modified signaling caused by bile acids, represents a dual mechanism of neurotoxicity in cirrhosis.

Manganese and Phenylethylamine

In addition to the well-known action of ammonia and bile acids described above, metallic products appear to be implicated in the pathogenesis of HE. Manganese is one of these potentially harmful metals, as it seems to bypass the liver through PSS and accumulate in the basal ganglia. Indeed, MRI scans in patients with HE have shown T1 hyperintensities, indicative of elevated manganese deposition. The characteristic extrapyramidal Parkinsonism seen in patients with cirrhosis has been ascribed to manganese's neurotoxic effect [19]. Except for manganese, research on gut-brain interactions in mice has shown that memory impairment, symmetric tremors, and neuronal loss, findings that align with those observed in cirrhotic patients, were associated with higher brain phenylethylamine (PEA) levels. The reduced monoamine oxidase-B activity in both the liver and serum due to cirrhosis may be the reason for PEA accumulation. At the same time, intestinal dysbiosis and *Ruminococcus gnavus* (*R. gnavus*) overgrowth, a gram-positive anaerobic bacterium, have been found to increase intestinal PEA production. The association between *R. gnavus* and PEA has been confirmed by the reversal of PEA-induced neurological symptoms in experimental models after successful treatment of *R. gnavus* [20].

Systemic and Neuroinflammation

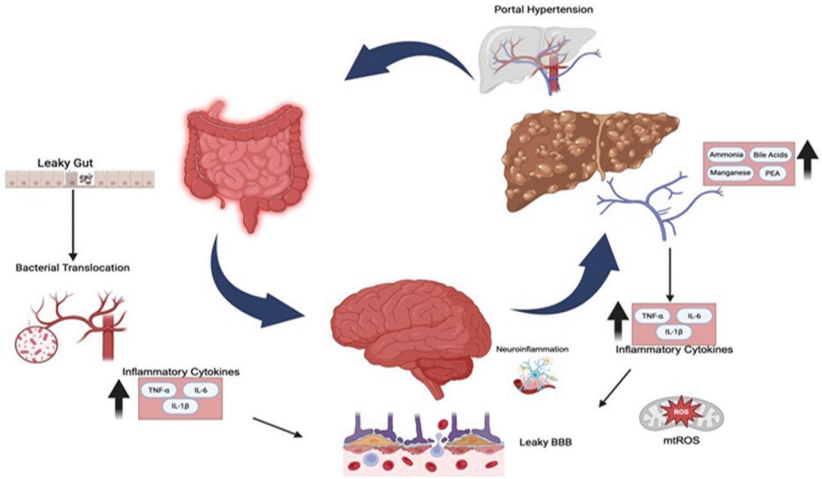
Portal endotoxemia increases the concentration of lipopolysaccharide and other pathogen-associated molecules in the systemic circulation, thereby affecting the brain through a compromised BBB. This rise in harmful substances triggers the production of pro-inflammatory cytokines such as interleukine (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β, which were associated with the severity of HE [21, 22]. Additionally, hyperammonemia also contributes to the systemic inflammation in cirrhosis by increasing mitochondrial reactive oxygen species (mtROS), which act as a "signal 2" for the activation of the nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome in microglia. The 2023 HE models using bile duct-ligated (BDL) rats suggest that hyperammonemia and neuroinflammation are not distinct mechanisms of HE but rather act synergistically [23]. Fig. 1 depicts the mechanisms underlying the pathogenesis of HE.

THE EMERGING ROLE OF THE GLYMPHATIC SYSTEM IN THE PATHOGENESIS OF HEPATIC ENCEPHALOPATHY

Structural and Regulatory Framework of the GS

Macro Anatomical Pathways

In the central nervous system (CNS), the glymphatic pathway serves as a fluid transport network that removes intercellular and metabolic waste. Initially, the cerebrospinal



In liver cirrhosis, portal hypertension contributes to increased intestinal permeability (leaky gut) and the increased circulation of inflammatory cytokines, resulting from bacterial translocation and the consequent activation of the immune system. On the other hand, liver dysfunction, along with PSS, leads to the accumulation of circulating cytokines and potentially toxic metabolites due to reduced liver clearance. All these factors compromise the BBB function, resulting in a leaky BBB.
BBB; Blood Brain Barrier, PEA; Phenylethylamine, TNF-α; Tumor Necrosis Factor Alpha, IL-6: Interleukin 6. IL-1ß: Interleukin 1β, mtROS; Mitochondrial Reactive Oxygen Species, PSS; Porto Systemic Shunting. Created with BioRender.com.

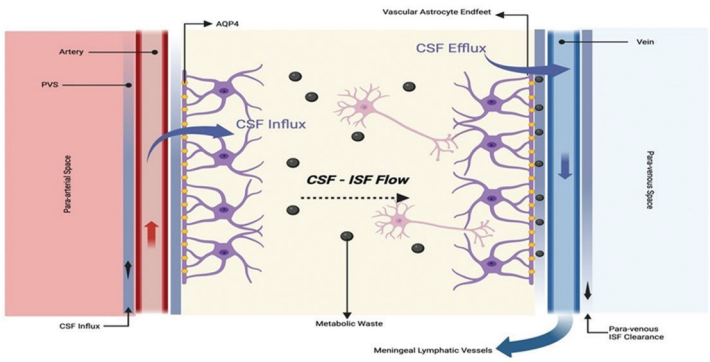
Fig. 1. The gut-liver-brain axis.

fluid (CSF) enters the subarachnoid space and permeates the brain parenchyma through the Virchow-Robin spaces (VRS) of the perivascular space (PVS). Within the parenchyma, there is an exchange between the CSF and the interstitial fluid (ISF). Subsequently, the flow reverses and is directed outward along para-venous pathways, completing a para-arterial/para-venous loop that constitutes the central conduit of the glymphatic circulation. These three sequential steps are described in detail in a 2022 neuroimaging review as a) para-arterial CSF inflow, b) interstitial transport mediated by aquaporin-4 (AQP4), and c) para-venous ISF outflow [24]. The fluid then exits the cranial cavity through the meningeal lymphatic vessels, completing the connection between the intracranial and systemic lymphatic compartments [25, 26] (Fig. 2).

The primary mechanism driving CSF flow into these macroscopic transport channels is pulsation of the cerebral arteries, which is driven by arterial wall movement. Evidence supporting this is the correlation observed between CSF velocity peaks and the R wave on the electrocardiogram, as well as the relationship between arterial wall velocity and CSF inflow velocity [27].

Molecular Gatekeepers

The accumulation of AQP4 at the terminal ends of astrocytes plays a crucial role in GS function. Specifically, the expression of AQP4 water channels facilitates the CSF transport. Mice with genetic deletion of *AQP4* (*AQP4* KO) have been found to exhibit both structural disorders and abnormalities in CSF-ISF molecular transport. Using diffusion-weighted magnetic resonance imaging (MRI), researchers observed that *AQP4* KO mice had increased overall brain volume and interstitial space, resulting in higher water content and lower CSF content, despite comparable CSF production and vascular density. Reduced CSF transport in the absence of AQP4 is likely due to reduced glymphatic clearance, leading to swelling and fluid retention in the interstitial space [28]. A-syntrophin (Snta) 1, encoded by the *SNTA1* gene, is a dystrophin-associated protein that functions as a key regulator



CSF from the para-arterial PVS flows through the arterial lumen and, aided by AQP4, enters the interstitial space. There, an exchange occurs between the CSF and the ISF, leading to CSF clearance of metabolic waste. Afterwards, CSF, mediated by AQP4 activation, exits into the para-venous PVS.
CSF: Cerebrospinal Fluid; PVS: Perivascular Space; AQP4: Aquaporin-4; ISF: Interstitial Fluid. Created with BioRender.com.

Fig. 2. Macro anatomical pathways of the glymphatic system.

of voltage-gated sodium channels [29]. *Snta1* significantly affects AQP4 function and, therefore, glymphatic clearance. Studies in *Snta1*-knockout rodents, which lack perivascular AQP4 localization, have demonstrated slow CSF inflow and tracer efflux, cognitive impairment, and elevated amyloid beta (Aβ) levels [30].

Dynamic Modulators

The GS's performance varies throughout the day. A 2020 study conducted on mice showed that substance exchange within the GS follows endogenous and circadian rhythms, peaking during the mid-rest phase. The same study also revealed differences in influx and efflux rates, specifically an increase during the day and a decrease at night. In *AQP4* KO mice, no day/night difference in glymphatic flow was observed. Additionally, daily and nocturnal changes in AQP4 localization were observed under both light and dark conditions, supporting the hypothesis that GS function depends on the circadian rhythm via AQP4 localization [31].

Another factor that may enhance brain waste removal is maintaining a proper body posture. Studies in rodents have shown that lateral position, which resembles their natural resting position, is more effective for waste management than the prone position [32]. It appears that body orientation affects arterial pulsatility, thereby regulating cerebral blood flow and the effectiveness of waste removal [32].

Autonomic Regulation of the GS

The autonomic nervous system (ANS) influences the functioning of the GS, primarily through its regulatory capacity over CSF flow in the subarachnoid space, the neurovascular coupling, and the removal of metabolic waste products [33]. An increase in norepinephrine, through activation of the sympathetic nervous system (SNS), appears to negatively affect GS function [34]. In liver failure, sympathetic tone increases and parasympathetic tone decreases [35, 36]. The main mechanisms that activate the SNS include visceral vasodilation, reduction in circulating volume, and chronic systemic inflammation, often accompanied by bacterial translocation, which is commonly observed in cirrhosis [37–41]. Conversely, vagus nerve stimulation (VNS), which activates the parasympathetic system, combined with the administration of a selective inhibitor of norepinephrine release (dexmedetomidine), improved glymphatic function in the hippocampus of mildly anesthetized rats [42].

Hepatic Drivers of Glymphatic Dysfunction

Hemodynamic Impairment

In liver cirrhosis, portal hypertension and the concomitant splanchnic vasodilation lead to reduced blood pressure and hemodynamic instability. This condition is not compensated by an adequate increase in heart rate and cardiac stroke as expected, due to an impaired cardiac function observed in cirrhosis. This cardiac dysfunction is referred to as cirrhotic cardiomyopathy and is characterized by blunted ventricular diastolic relaxation, systolic dysfunction in response to stress stimuli, and electrophysiological abnormalities, more frequently presented as a prolonged QT interval [43, 44]. As previously noted, splanchnic vasodilation is mediated by increased circulating vasodilatory factors attributable to interstitial bacterial overgrowth, increased bacterial translocation, and reduced clearance of these factors due to liver failure and PSS [45]. In turn, splanchnic vasodilation leads to volume redistribution, central hypovolemia, and ultimately impaired cerebral perfusion. Because one mechanism regulating GS function is pulsatile cerebral arterial blood flow, disruptions in blood flow may contribute to glymphatic flow dysfunction. Notably, a study using transcranial Doppler ultrasound to examine hemodynamic changes in cerebral blood flow among 100 participants, 50 with decompensated cirrhosis and 50 healthy individuals, showed that patients with cirrhosis had lower mean flow velocity, higher pulsatility index (PI), and higher resistance index (RI), indicating reduced cerebral autoregulation [46].

Sleep Disruption

The importance of sleep for the proper functioning of the GS is well established [47]. A 2020 study of 1,098 patients with cirrhosis found that sleep disorders were present even before the onset of HE, including among those classified in the Child-Pugh A stage. Poor nighttime sleep and excessive daytime sleepiness were strongly associated with the Child-Pugh stage, with stage C showing greater severity than stage A. There was also a notable risk for obstructive sleep apnea and the presence of generalized anxiety disorder [48]. Polysomnographic studies have confirmed that cirrhotic patients exhibit reduced slow-wave (N3) and REM sleep, along with a higher arousal index, compared with healthy controls [49, 50].

Hyponatremia

Hyponatremia is the most common electrolyte disorder observed in cirrhosis. The reduction in effective circulating volume because of splanchnic vasodilation caused by portal hypertension leads to the secretion of antidiuretic hormone (ADH). This results in marked water retention, which greatly exceeds sodium retention, thereby diluting plasma sodium [51]. In cirrhosis-induced hyponatremia, the extracellular fluid becomes hypotonic; consequently, water shifts into brain cells via osmosis, leading to cytotoxic edema [52]. The resulting astrocyte swelling compresses the PVS, potentially exacerbating glymphatic dysfunction [53]. Using rat models of induced systemic hyponatremia, Lim et al. [54] demonstrated, by immunoblotting, that AQP4 expression in the cerebral cortex is downregulated as a compensatory mechanism against cerebral edema. This alteration induces a loss of astrocytic polarity, thereby fundamentally impairing glymphatic clearance.

EXPERIMENTAL AND CLINICAL MODELS LINKING GLYMPHATIC DYSFUNCTION AND HEPATIC ENCEPHALOPATHY

Preclinical Models

In BDL rats, glymphatic flow was assessed using contrast-enhanced MRI and mass spectrometry. Additionally, AQP4 immunofluorescence and behavioral experiments were conducted. The studies not only demonstrated an association between disruption of glymphatic flow and the development

of HE but also identified specific brain regions, including the olfactory bulb, prefrontal cortex, and hippocampus, in which impaired glymphatic clearance was observed. These impairments were associated with cognitive and behavioral changes indicative of HE. Furthermore, AQP4 immunofluorescence revealed reduced expression, particularly in the olfactory bulb and prefrontal cortex, suggesting glymphatic dysfunction [55].

On the other hand, experimental data in rats with acute liver failure indicated that AQP4 levels increase at the plasma membrane, while its concentration and mRNA levels in tissues remain unchanged. These findings suggest that the increase in AQP4 is not due to enhanced transcription but rather to its more stable binding to the plasma membrane or its reduced degradation. The elevated levels of AQP4 at the perivascular ends of astrocytes likely exacerbate the development of cerebral edema in acute liver failure, further worsening HE [56].

The BBB disorder has been observed in both animal models and patients with HE. Some studies support the hypothesis that BBB permeability increases in these cases, whereas others challenge it. This controversy likely stems from differences in the techniques used to evaluate the BBB across studies [57]. Regardless, BBB disruption leads to the accumulation of metabolic waste in brain tissue, contributing to the development of cerebral edema. This condition impairs AQP4 water channel function, disrupts GS function, and exacerbates HE [58-61].

Evidence of Glymphatic Slowdown in Cirrhotic Patients

Diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) has emerged as a crucial tool for assessing glymphatic flow. Higher DTI-ALPS values indicate a more intact GS, while lower values are associated with glymphatic dysfunction [62]. In a neuroimaging study involving a total of 70 subjects, 37 patients with untreated hepatitis B cirrhosis, divided into those with MHE and those without (non-MHE), and 33 healthy controls, participated. The MHE subgroup exhibited significantly lower DTI-ALPS values than the non-MHE and HC groups. Interestingly, white matter edema and glymphatic flow disorders were identified even in the early stages of hepatitis B-related cirrhosis [63]. Recent data from a cross-sectional study involving 46 pre-cirrhotic patients with metabolic-associated steatotic liver disease (MASLD) and 30 matched controls suggest that glymphatic dysfunction may occur before the onset of cirrhosis. In this study, patients with MASLD showed lower DTI-ALPS values than healthy controls. This finding may be linked to changes in cognitive function among these patients, and it appeared to be further exacerbated in those with metabolic syndrome [64].

In addition, an independent study was conducted to assess BBB permeability in patients with liver cirrhosis by evaluating KTRANS, a dynamic contrast-enhanced MRI parameter that quantifies blood–brain barrier permeability [65]. For this purpose, digital contrast-enhanced (DCE) MR perfusion and MR spectroscopy were used, whereas the psychometric HE score (PHES) was employed to determine HE. The study included 40 participants, divided into three groups: 17 patients with cirrhosis and covert HE, characterized by PHES ≤4; 13 patients without HE, with PHES>4; and 10 healthy controls. The KTRANS measurement in the frontal-parietal cortex indicated increased BBB permeability, with values of 0.01 ± 0.02 in the covert HE group, 0.005 ± 0.005 in the cirrhotic patients without HE, and 0.004 ± 0.002 in the healthy controls (p=0.032 across all three groups). This finding suggests delayed tracer washout in covert HE and impaired washout in non-HE [65]. Table I highlights the pathophysiological disorders linking liver cirrhosis to GS dysfunction, and Fig. 3 summarizes how this dysfunction predisposes to HE.

POTENTIAL FUTURE THERAPEUTHIC PERSPECTIVES

Current guidelines for the management of HE emphasize the need to address contributing factors, including infections, gastrointestinal bleeding, electrolyte imbalances, and constipation [66]. Furthermore, oral lactulose is recommended as monotherapy or in combination with rifaximin, as appropriate [67, 68]. However, these interventions may not fully resolve HE in a significant number of patients, with some individuals likely to experience recurrent HE episodes. As a result, there is an urgent need to develop innovative therapeutic strategies to improve patient outcomes. Targeting GS dysfunction may be crucial to addressing this challenge.

Table I. Pathophysiological mechanisms linking liver cirrhosis to glymphatic dysfunction

Affected Factor	Mechanism	Description	References
Hemodynamic Impairment	Splanchnic vasodilation and cirrhotic cardiomyopathy	Splanchnic vasodilation and reduced cardiac output lead to central hypovolemia, impaired cerebral autoregulation, and disruption of the arterial pulsatility, causing glymphatic dysfunction	[27, 43-46, 73-77]
Altered autonomic nervous system	SNS hyperactivity and vagal tone inhibition	Increased norepinephrine levels and SNS overstimulation cause dysfunction of the GS, whereas PNS stimulation may confer benefits to glymphatic clearance	[33-42]
Astrocytic dysfunction & AQP4 dysregulation	Cellular oedema, reduced AQP4 expression, and disruption of the BBB	Reduced AQP4 polarity leads to impaired clearance of toxic metabolites, causing cerebral oedema and diminished glymphatic clearance	[24, 28-31, 51, 52, 54-57, 69-72]
Sleep disturbances	Reduced deep and REM sleep	Paradoxical sleep is associated with memory impairment and cognitive decline.	[47-50, 78-80]

AQP4: Aquaporin 4; GS: glymphatic system; PNS: parasympathetic nervous system; SNS: sympathetic nervous system; BBB: blood-brain barrier; REM: rapid eye movement.

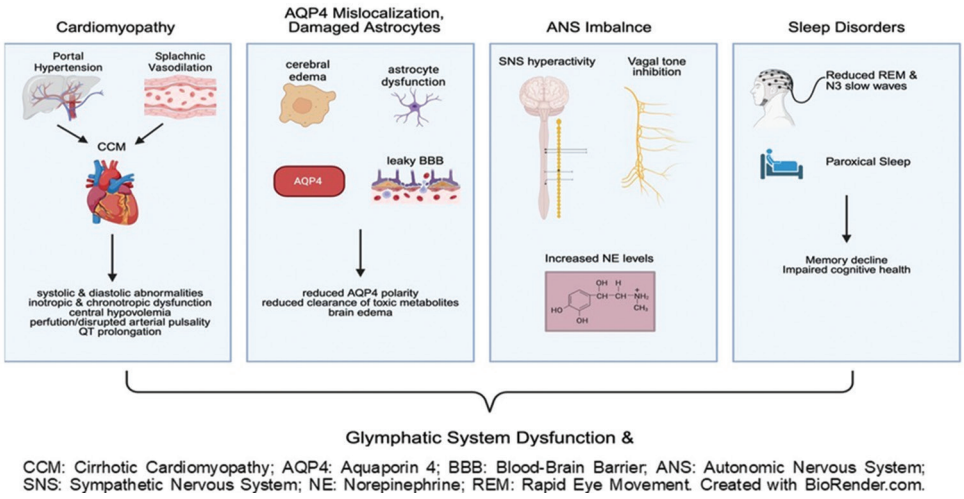


Fig. 3. The pathways through GS dysfunction contribute to the development of hepatic encephalopathy.

AQP4 Polarity Restoration

The most direct method to restore glymphatic circulation could be by stabilizing AQP4. In a rodent model of brain injury, administering melatonin and roscovitine restored perivascular AQP4. This enhancement enhances the interaction between AQP4 and Snta1 while inhibiting cyclin-dependent kinase 5 (CDK5) activity. The study's outcomes included improved neurological function, maintenance of an intact BBB, and reduced cerebral edema (69). Other molecules that target the AQP4 pathways have also been investigated. TGN-073, a small-molecule mediator, has been shown to facilitate AQP4, thereby increasing the circulation of interstitial fluid through the GS [70]. Conversely, TGN-020, an AQP4 inhibitor, appears to improve acute cytotoxic edema but may negatively affect glymphatic flow [71]. Moreover, GM6001, a matrix metalloproteinase-9 (MMP-9) inhibitor, has been shown to restore perivascular AQP4 integrity and reduce metabolic disorders [72].

Sleep & Circadian Rehabilitation

Non-pharmacological methods for restoring sleep in cirrhotic patients with HE or MHE should prioritize Cognitive Behavioral Therapy for Insomnia (CBT-I). Additionally, melatonin, histamine (H1) blockers, and circadian light therapy can be utilized [73-75]. The administration of intense light during the day, intended to synchronize melatonin levels, along with avoiding large evening meals before bedtime, has been studied in individual clinical cases and shown to be beneficial. However, these results require further validation through large randomized controlled trials (RCTs) [75]. A 2007 RCT, studying the effects of hydroxyzine, an H1 histamine inhibitor, demonstrated that the treatment group experienced a 35% increase in sleep efficiency compared to the control group [76].

ANS Stimulation

At present, there are no RCTs specifically examining ANS stimulation in cirrhotic patients. Nonetheless, a promising strategy is VNS, which can be achieved via transcutaneous auricular stimulation (taVNS) or by administering a selective inhibitor of norepinephrine release, such as dexmedetomidine [42, 77]. Additionally, non-selective β-blockers may have a role by mitigating sympathetic overactivity in a complementary manner [78, 79]. However, their use should be individualized, as observational studies have identified an association between non-selective β-blockers and increased hospital readmissions for HE [80].

DISCUSSION

Until recently, the GS had not been strongly associated with HE. Experimental evidence in this area remains limited, and existing reviews have mainly focused on astrocytic injury, often overlooking other relevant pathophysiological mechanisms. This review presents an emerging pathophysiological framework for HE, emphasizing how glymphatic dysfunction connects the gut–liver–brain axis, hemodynamic alterations, ANS imbalances, and circadian rhythm disturbances in patients with cirrhosis. While it does not propose specific research protocols or therapeutic interventions, this review identifies key mechanistic pathways and unresolved questions that expand the current conceptual perspective and pave the way for future research. Such efforts are essential for developing improved diagnostic tools and targeted treatment strategies.

Currently, most available data derive from preclinical models, such as BDL rodents, where decreased glymphatic clearance and disturbances in *AQP4* expression and localization have been observed. However, the relevance of these findings to human populations must be approached with caution. In limited human studies, DTI-ALPS suggests that glymphatic function declines in patients with MHE. Additionally, DCE-MRI using KTRANS has documented increased BBB permeability in cirrhotic patients. Nonetheless, the small and heterogeneous samples in these studies limit their generalizability.

Given the limited human data, the assessment of GS function in routine clinical practice remains inconclusive,

particularly regarding its role in HE. However, a better understanding of glymphatic dysfunction may elucidate why certain patients experience chronic, refractory HE or episodes of HE without identifiable precipitating factors. Such insights could facilitate the development of novel pharmacological interventions to restore glymphatic function, potentially alleviating symptoms and improving patients' quality of life.

Today, there is no universally accessible method for directly assessing glymphatic dysfunction in clinical settings. Available imaging techniques require specialized technical expertise, and in some cases, prolonged acquisition times limit routine applicability. Among these, DTI-ALPS appears to be a promising non-invasive modality for clinical incorporation, given its relative time efficiency compared with contrast-based techniques such as dynamic contrast-enhanced MRI. In addition, no specific serum biomarkers have been validated for the direct assessment of glymphatic clearance. While markers of astrocytic injury, such as glial fibrillary acidic protein (GFAP) and S100 calcium-binding protein B (S100B), may provide indirect evidence of glymphatic dysfunction in cirrhosis, their diagnostic value has yet to be confirmed in large-scale clinical studies. Standardized imaging protocols and harmonized analytical pipelines are crucial for ensuring reproducibility and facilitating translation into clinical practice.

Despite progress in our understanding of glymphatic function, significant knowledge gaps persist. Specifically, it remains uncertain whether glymphatic dysfunction is exacerbated during infections, which commonly serve as a trigger for HE in patients with cirrhosis. It is of particular interest to examine whether systemic inflammation and infection-induced hemodynamic instability further compromise glymphatic clearance, thereby heightening the risk of HE. Additionally, the influence of comorbid conditions, such as diabetes mellitus and neurodegenerative disorders, on glymphatic function in individuals with cirrhosis has yet to be adequately investigated.

Current HE management guidelines primarily emphasize supportive care and control of precipitating factors. Targeted strategies to restore glymphatic function are not yet available. Potential approaches, including stabilization of *AQP4* polarity, circadian rhythm modulation, and enhancement of parasympathetic activity, remain at the experimental or preclinical stage, and randomized controlled trials involving cirrhotic patients with HE have not yet been conducted.

CONCLUSIONS

Dysfunction of the GS provides a compelling integrative framework encompassing various mechanisms implicated in HE. Despite promising preclinical evidence and emerging human data, significant gaps remain before clinical implementation can be considered. Current diagnostic methodologies are often technically demanding and not widely accessible. Therefore, well-structured multicenter RCTs are imperative to ascertain whether therapeutic targeting of GS can substantially enhance outcomes for patients diagnosed with liver cirrhosis and HE.

Conflicts of interest: None to declare.

Authors' contribution: E.L.K. and D.S.K conceived and designed the study. E.L.K., N.D.K., G.P. and T.A. collected data. E.L.K, T.A. drafted the manuscript. N.D.K., G.P. and T.A. revised the manuscript. D.S.K critically revised the manuscript for important intellectual content. All the authors read and approved the final manuscript.

REFERENCES

1. Lima LCD, Miranda AS, Ferreira RN, Rachid MA, e Silva ACS. Hepatic encephalopathy: Lessons from preclinical studies. World J Gastroenterol. 2019;11:173–85. doi:https://pubmed.ncbi.nlm.nih.gov/30820267/
2. Sørensen M, Lauridsen MM, Montagnese S. The social and psychological impact of hepatic encephalopathy. Metab Brain Dis. 2024;39:1227–30. doi:10.1007/s11011-024-01384-x
3. Weissenborn K. Hepatic encephalopathy: definition, clinical grading and diagnostic principles. Drugs. 2019;79:5–9. doi:10.1007/s40265-018-1018-z
4. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the AASLD and EASL. Hepatology. 2014;60:715–35. doi:10.1002/hep.27210
5. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy-definition, nomenclature, diagnosis, and quantification. Hepatology. 2002;35:716–21.doi:10.1053/jhep.2002.31250
6. Bajaj JS. The role of microbiota in hepatic encephalopathy. Gut Microbes. 2014;5:397–403. doi:10.4161/gmic.28684
7. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis. Ann Gastroenterol. 2015;28:203–209. https://pmc.ncbi.nlm.nih.gov/articles/PMC4367209/
8. Felipo V. Hepatic encepalopathy: effects of liver failure on brain function. Nat Rev Neurosci. 2013;14:851-858. doi: 10.1038/nrm3587.
9. Albillos A, de Gottardi A, Rescigno M. The gut–liver axis in liver disease. J Hepatol. 2020;72:558–77. doi:10.1016/j.jhep.2019.10.003
10. Tripathi A, Debelius J, Brenner DA, et al. The gut–liver axis and the microbiome. Nat Rev Gastroenterol Hepatol. 2018;15:397–411. doi:10.1038/s41575-018-0011-z
11. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The microbiota–gut–brain axis. Physiol Rev. 2019;99:1877–2013. doi:10.1152/physrev.00018.2018
12. Wiest R, Albillos A, Trauner M, Bajaj JS, Jalan R. Targeting the gut–liver axis in liver disease. J Hepatol. 2017;67:1084–103. doi:10.1016/j.jhep.2017.05.007
13. Dicks LMT. Gut bacteria and neurotransmitters. Microorganisms. 2022;10:1838. doi:10.3390/microorganisms10101838
14. Claeys W, Van Hoecke L, Lefere S, et al. The neurogliovascular unit in hepatic encephalopathy. JHEP Reports. 2021;3:100260. doi:10.1016/j.jhepr.2021.100352
15. Ahluwalia V, Betrapally NS, Hylemon PB, et al. Impaired gut–liver–brain axis in cirrhosis. Sci Rep. 2016;6:26800. doi:10.1038/srep26800
16. Sepehrinezhad A, Stolze Larsen F, Ashayeri Ahmadabad R, Shahbazi A, Sahab Negah S. The glymphatic system in hepatic encephalopathy. Cells. 2023;12:979. doi:10.3390/cells12070979
17. Sepehrinezhad A, Zarifkar A, Namvar G, Shahbazi A, Williams R. Astrocyte swelling in hepatic encephalopathy. Metab Brain Dis. 2020;35:559–78. doi:10.1007/s11011-020-00549-8
18. Williams E, Chu C, DeMorrow S. Bile acids and their receptors in hepatic encephalopathy. Anal Biochem. 2021;643:114436. doi:10.1016/j.ab.2021.114436

19. Butterworth RF. Hepatic encephalopathy in cirrhosis: pathology and pathophysiology. Drugs. 2019;79:17–21. doi:10.1007/s40265-018-1048-1
20. He X, Hu M, Xu Y, et al. The gut–brain axis underlying hepatic encephalopathy in cirrhosis. Nat Med. 2025;31:627–38. https://www.nature.com/articles/s41591-024-03405-9
21. Efremo va I, Maslennikov R, Kudryavtseva A, et al. Gut microbiota and cytokine profile in cirrhosis. J Clin Transl Hepatol. 2024;12:689–97. doi:10.14218/JCTH.2024.00090
22. Wang LQ, Zhou HJ, Pan CF, Zhu SM, Xu LM. Expression of IL1β, IL6, and TNFα in rats with thioacetamide induced acute liver failure and encephalopathy: correlation with brain edema. Asian Biomed. 2011;5:205–15. https://reference-global.com/download/article/10.5372/1905-7415.0502.026.pdf
23. Cheon SY, Kim MY, Kim J, et al. Hyperammonemia induces microglial NLRP3 inflammasome activation via mitochondrial oxidative stress in hepatic encephalopathy. Biomed J. 2023;46:100–12. doi:10.1016/j.bj.2023.04.001
24. Yu L, Hu X, Li H, Zhao Y. Perivascular spaces, glymphatic system and MR. Front Neurol. 2022;13:xxxx. doi:10.3389/fneur.2022.844938
25. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. Nature. 2015;523:337–41. doi:10.1038/nature14432
26. Aspelund A, Antila S, Proulx ST, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J Exp Med. 2015;212:991–9. doi:10.1084/jem.20142290
27. Mestre H, Tithof J, Du T, et al. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. Nat Commun. 2018;9:4878. https://www.nature.com/articles/s41467-018-07318-3
28. Gomolka RS, Hablitz LM, Mestre H, et al. Loss of aquaporin4 results in dysfunction of the glymphatic system via brainwide interstitial fluid stagnation. Elife. 2023;12:exxxx. doi:10.7554/eLife.82232
29. Choi JI, Wang C, Thomas MJ, Pitt GS. α1Syntrophin variant identified in druginduced long QT syndrome increases late sodium current. PLoS One. 2016;11:e0152355. doi:10.1371/journal.pone.0152355
30. Bojarskaite L, Nafari S, Ravnanger AK, et al. Role of aquaporin4 polarization in extracellular solute clearance. Fluids Barriers CNS. 2024;21:1–10. doi:10.1186/s12987-024-00527-7
31. Hablitz LM, Plá V, Giannetto M, et al. Circadian control of brain glymphatic and lymphatic fluid flow. Nat Commun. 2020;11:4411. doi:10.1038/s41467-020-18115-2
32. Lee H, Xie L, Yu M, et al. The effect of body posture on brain glymphatic transport. J Neurosci. 2015;35:11034–44. doi:10.1523/JNEUROSCI.1625-15.2015
33. Picchioni D, Özbay PS, Mandelkow H, et al. Autonomic arousals contribute to brain fluid pulsations during sleep. Neuroimage. 2022;249:118863. doi:10.1016/j.neuroimage.2022.118888
34. Jessen NA, Munk ASF, Lundgaard I, Nedergaard M. The glymphatic system – a beginner's guide. Neurochem Res. 2015;40:2583–99. doi:10.1007/s11064-015-1581-6
35. Oyelade T, Canciani G, Bottaro M, et al. Heart rate turbulence predicts survival independently from severity of liver dysfunction in patients with cirrhosis. Front Physiol. 2020;11:602456. doi:10.3389/fphys.2020.602456
36. Ates F, Topal E, Kosar F, et al. The relationship of heart rate variability with the severity and prognosis of cirrhosis. Dig Dis Sci. 2006;51:1614–8. doi:10.1007/s10620-006-9073-9
37. Lan T, Chen M, Tang C, Deltenre P. Recent developments in the management of ascites in cirrhosis. United European Gastroenterol J. 2024;12:261–72. doi:10.1002/ueg2.12539
38. Fede G, Privitera G, Tomaselli T, Spadaro L, Purrello F. Cardiovascular dysfunction in patients with liver cirrhosis. Ann Gastroenterol. 2015;28:31–40. https://pubmed.ncbi.nlm.nih.gov/25608575/
39. Moore CM, Van Thiel DH. Cirrhotic ascites review: pathophysiology, diagnosis and management. World J Hepatol. 2013;5:251–63. doi:10.4254/wjh.v5.i5.251
40. Kronsten VT, Shawcross DL. Clinical implications of inflammation in patients with cirrhosis. Am J Gastroenterol. 2024;120:65–78. doi:10.14309/ajg.0000000000003056
41. Simbrunner B, Caparrós E, Neuwirth T, et al. Bacterial translocation occurs early in cirrhosis and triggers a selective inflammatory response. Hepatol Int. 2023;17:1045–56. doi:10.1007/s12072-023-10496-y
42. Cheng KP, Brodnick SK, Blanz SL, et al. Clinically derived vagus nerve stimulation enhances cerebrospinal fluid penetrance. Brain Stimul. 2020;13:1024–30. doi:10.1016/j.brs.2020.03.012
43. Karagiannakis DS, Papatheodoridis G, Vlachogiannakos J. Recent advances in cirrhotic cardiomyopathy. Dig Dis Sci. 2015;60:1141–51. doi:10.1007/s10620-014-3432-8
44. Karagiannakis DS, Stefanaki K, Anastasiadis G, Voulgaris T, Vlachogiannakos J. Prevalence of cirrhotic cardiomyopathy according to different diagnostic criteria: alterations in ultrasonographic parameters of both left and right ventricles before and after stress. Ann Gastroenterol. 2023;36:564–72. doi:10.20524/aog.2023.0824
45. Møller S, Bendtsen F. The pathophysiology of arterial vasodilatation and hyperdynamic circulation in cirrhosis. Liver Int. 2018;38:570–80. doi:10.1111/liv.13589
46. Öncel Ç, Yilmaz M. Cerebral hemodynamics in patients with cirrhosis. Turk J Gastroenterol. 2016;27:264–7. doi:10.5152/tjg.2016.15446
47. Ma J, Chen M, Liu GH, et al. Effects of sleep on glymphatic functioning and multimodal brain networks affecting memory in older adults. Mol Psychiatry. 2025;30:1717–29. doi:10.1038/s41380-024-02778-0
48. Kumar M, Kainth S, Kumar S, et al. Prevalence of and factors associated with sleep–wake abnormalities in patients with cirrhosis. J Clin Exp Hepatol. 2021;11:453–65. doi:10.1016/j.jceh.2020.10.006
49. Liu C, Zhou J, Yang X, et al. Changes in sleep architecture and quality in minimal hepatic encephalopathy patients and relationship to psychological dysfunction. Int J Clin Exp Med. 2015;8:21541–8. https://pubmed.ncbi.nlm.nih.gov/26885103/
50. Badal BD, Bajaj JS. Whoop there it is: decoding sleep, cirrhosis, and HE. Hepatol Commun. 2023;7:e0071. doi:10.1097/HC9.0000000000000071
51. John S, Thuluvath PJ. Hyponatremia in cirrhosis: pathophysiology and management. World J Gastroenterol. 2015;21:3197–205. doi:10.3748/wjg.v21.i11.3197
52. Nathan BR. Cerebral correlates of hyponatremia. Neurocrit Care. 2007;6:72–8. doi:10.1385/NCC:6:1:72
53. Nedergaard M, Goldman SA. Glymphatic failure as a final common pathway to dementia. Science. 2020;370:50–6. doi:10.1126/science.abb8739
54. Lim JH, Yong J, Jung W, Park HS, Lim JH, Jung YW, et al. Different expressions of AQP1 and AQP4 in hyponatremic rat brain. Int J Morphol. 2021;39:64–9. https://www.scielo.cl/pdf/ijmorphol/v39n1/0717-9502-ijmorphol-39-01-64.pdf
55. Hadjihambi A, Harrison IF, CostasRodríguez M, et al. Impaired brain glymphatic flow in experimental hepatic encephalopathy. J Hepatol. 2019;70:40–9. doi:10.1016/j.jhep.2018.08.021
56. Rama Rao KV, Jayakumar AR, Tong X, Curtis KM, Norenberg MD. Brain aquaporin4 in experimental acute liver failure. J Neuropathol Exp Neurol. 2010;69:869–79. doi:10.1097/NEN.0b013e3181ebe581

57. Skowrońska M, Albrecht J. Alterations of blood–brain barrier function in hyperammonemia: an overview. Neurotox Res. 2012;21:236–44. doi:10.1007/s12640-011-9269-4
58. Weiss N, Rosselli M, Mouri S, et al. Modification in CSF specific gravity in acutely decompensated cirrhosis and acuteonchronic liver failure. Metab Brain Dis. 2017;32:369–76. doi:10.1007/s11011-016-9916-9
59. Chen F, Ohashi N, Li W, Eckman C, Nguyen JH. Disruptions of occludin and claudin5 in brain endothelial cells in vitro and in mice with acute liver failure. Hepatology. 2009;50:1914–23. doi:10.1002/hep.23203
60. Weiss N, Barbier SaintHilaire P, Colsch B, et al. Cerebrospinal fluid metabolomics highlights dysregulation of energy metabolism in overt hepatic encephalopathy. J Hepatol. 2016;65:1120–30. doi:10.1016/j.jhep.2016.07.046
61. Nguyen JH, Yamamoto S, Steers J, et al. Matrix metalloproteinase9 contributes to brain extravasation and edema in fulminant hepatic failure mice. J Hepatol. 2006;44:1105–14. doi:10.1016/j.jhep.2005.09.019
62. Clark O, DelgadoSanchez A, Cullell N, Correa SAL, Krupinski J, Ray N. Diffusion tensor imaging analysis along the perivascular space in the UK Biobank. Sleep Med. 2024;119:399–405. doi:10.1016/j.sleep.2024.05.007
63. Ju C, Yang L, Dai Z, Wang Y, Li C, Zhao W, et al. Associations among neuropsychological performance, brain structural alterations, and glymphatic function in minimal hepatic encephalopathy. Brain Res Bull. 2025;228:106–15. doi:10.1016/j.brainresbull.2025.111416
64. Shu K, Fu YC, Huang M, et al. Altered brain glymphatic function at diffusion tensor MRI in precirrhotic metabolic dysfunction associated fatty liver disease. Acad Radiol. 2024;31:4946–54. doi:10.1016/j.acra.2024.06.022
65. Chaganti J, Zeng G, Tun N, et al. Novel magnetic resonance KTRANS measurement of blood–brain barrier permeability correlated with covert hepatic encephalopathy. Hepatol Commun. 2023;7:e0106. doi:10.1097/HC9.0000000000000079
66. Montagnese S, Rautou PE, RomeroGómez M, et al. EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. J Hepatol. 2022;77:807–24. doi:10.1016/j.jhep.2022.06.001
67. Bloom PP, Tapper EB. Lactulose in cirrhosis: efficacy, mechanism, and practical considerations. Hepatol Commun. 2023;7:e0295. doi:10.1097/HC9.0000000000000295
68. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatic encepalopathy. J Hepatol. 2022;77:807-824. doi: 10.1016/j.jhep.2022.06.001
69. Li Y, Ye Q, Lu W, et al. Melatonin enhances aquaporin4 and αsyntrophin interaction by inhibiting cyclin-dependent kinase 5 to preserve glymphatic function in neonatal hypoxic ischemic encephalopathy. J Pineal Res. 2025;77:e70063. doi:10.1111/jpi.70063
70. Huber VJ, Igarashi H, Ueki S, Kwee IL, Nakada T. Aquaporin4 facilitator TGN073 promotes interstitial fluid circulation within the blood–brain barrier: [17O]H_2O JJVCPE MRI study. Neuroreport. 2018;29:697–703. doi:10.1097/WNR.0000000000000990
71. Sun C, Lin L, Yin L, et al. Acutely inhibiting AQP4 with TGN020 improves functional outcome by attenuating edema and peri-infarct astrogliosis after cerebral ischemia. Front Immunol. 2022;13:870029. doi:10.3389/fimmu.2022.870029
72. Si X, Dai S, Fang Y, et al. Matrix metalloproteinase-9 inhibition prevents aquaporin-4 depolarizationmediated glymphatic dysfunction in Parkinson's disease. J Adv Res. 2024;56:125–36. doi:10.1016/j.jare.2023.03.004
73. Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: AASM clinical practice guideline. J Clin Sleep Med. 2021;17:255–62. doi:10.5664/jcsm.8986
74. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: ACP clinical guideline. Ann Intern Med. 2016;165:125–33. doi:10.7326/M15-2175
75. Zhao X, Wong P. Managing sleep disturbances in cirrhosis. Scientifica (Cairo). 2016;2016:6576812. doi:10.1155/2016/6576812
76. Spahr L, Coeytaux A, Giostra E, Hadengue A, Annoni JM. Histamine H1 blocker hydroxyzine improves sleep in cirrhosis and minimal hepatic encephalopathy: randomized controlled pilot trial. Am J Gastroenterol. 2007;102:744–53. doi:10.1111/j.1572-0241.2006.01028.x
77. Farmer AD, Strzelczyk A, Finisguerra A, et al. International consensus recommendations for minimum reporting standards in research on transcutaneous vagus nerve stimulation (Version 2020). Front Hum Neurosci. 2021;14:568051. doi:10.3389/fnhum.2020.568051
78. Karagiannakis DS, Karakousis ND, Androutsakos T. β-blockers in liver cirrhosis: a wonder drug for every stage of portal hypertension? Biomedicines. 2023;12:57. doi:10.3390/biomedicines12010057
79. de Franchis R, Bosch J, GarciaTsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII – renewing consensus in portal hypertension. J Hepatol. 2022;76:959–74. doi:10.1016/j.jhep.2021.12.022
80. Fallahzadeh MA, Asrani SK, Tapper EB, Saracino G, Rahimi RS. Non-selective beta-blocker use is associated with increased hepatic encephalopathy-related readmissions in cirrhosis. World J Clin Cases. 2022;10:8097–106. doi:10.12998/wjcc.v10.i23.8097