

Electroencephalography in hepatic encephalopathy: diagnostic and prognostic applications across the disease spectrum

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Abstract

Hepatic encephalopathy (HE) represents a neuropsychiatric continuum arising from cirrhosis and portosystemic shunting, where metabolic toxicity, neuroinflammation and impaired cerebral autoregulation progressively disrupt cortical network function. Minimal hepatic encephalopathy (MHE), its first and not overt stage, has been recognized as a major cause of impaired quality of life and has been associated with reduced functioning and heightened risk of progression to overt HE and mortality. Current diagnostic tools, primarily psychometric tests, capture only clinical manifestations, and lack the ability to directly examine neuronal dysfunction. Electroencephalography (EEG) provides a real-time tool to quantify brain activity, allowing the identification of subtle neural alterations long before clinical symptoms appear. Quantitative EEG (qEEG) indices, such as reduced mean dominant frequency, increased slow-wave activity and disrupted spectral ratios, consistently reflect early cognitive impairment in studies, and are correlated with liver disease severity and neurological performance. These markers not only enhance the early diagnosis of MHE, but also carry important prognostic implications: several EEG parameters have independently predicted future progression of the disease, hospitalization and mortality, and may enhance established risk models when integrated into multicomponent indices such as model for end-stage liver disease (MELD)-EEG. Collectively, evidence suggests that EEG could be used as a multidimensional and objective assessment of neural dysfunction that complements psychometric, biochemical, and imaging-based methods. Our study aimed to examine the diverse electrophysiological findings clarifying the diagnostic and prognostic importance of EEG-based markers, and to examine their possible role in early diagnosis, risk stratification and future clinical applications for patients with HE.

Keywords Cirrhosis, hepatic encephalopathy, mean dominant frequency, electroencephalography, fast Fourier transform

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Introduction

Cirrhosis reflects a more advanced stage of chronic liver disease, defined by extensive fibrosis, architectural distortion and regenerative nodule formation, impairing hepatic capacity and portal blood flow [1]. It is responsible for over 1 million deaths annually, ranking among the leading causes of mortality and imposing a significant burden on health systems worldwide [2]. Its clinical burden varies by region—cirrhosis is the 9th leading cause of mortality in Southeast Asia and Europe [3]. The most common etiologies of cirrhosis in the world include excessive alcohol consumption, metabolic dysfunction-associated steatotic liver disease, and chronic hepatitis B and C infections [4,5]. Alcohol-related liver disease

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is the principal cause of cirrhosis in Europe, accounting for significant morbidity and economic loss [6].

The clinical course of cirrhosis is divided into 2 main stages, compensated and decompensated, with the latter manifesting as complications such as ascites, variceal bleeding and hepatic encephalopathy (HE) [7]. In the decompensated stage, splanchnic arterial vasodilation stimulates endogenous vasoconstrictor pathways, leading to renal fluid retention that causes the development of ascites [8]. Nitric oxide-mediated circulatory derangements reduce mitochondrial ATP production, causing systemic inflammation that leads to immune-mediated tissue injury and metabolic alterations, culminating in multiorgan dysfunction [9]. Progressive fibrosis disrupts the sinusoidal architecture, increasing intrahepatic vascular resistance and reducing nitric oxide within the liver, while enhanced splanchnic vasodilation further elevates portal pressure, leading to the major complications of the disease [10].

Prognosis is based on scoring systems, such as the Child-Pugh score, which evaluates encephalopathy, ascites, bilirubin, albumin and prothrombin time, offering semi-quantitative risk stratification [11]. The model for end-stage liver disease (MELD) score, initially measuring serum bilirubin, creatinine and international normalized ratio, is recognized as the main tool for assessing short-term mortality and prioritizing transplant allocation, whereas the updated version, MELD-Na, which incorporates serum sodium, has proven even more accurate in prognostic assessments [12,13]. Biomarkers based on albumin have recently emerged as valuable tools for stratifying disease severity and prognosis compared to traditional markers [14], while imaging methods such as transient elastography also contribute to noninvasive detection and staging [15]. Newly recognized prognostic systems enhance risk prediction by integrating organ failure metrics, inflammatory markers, and early decompensation predictors [16]. Artificial intelligence-based models have also gained prominence in cirrhosis prognosis, enabling a dynamic multimodal risk assessment challenging the static capabilities of conventional scoring systems [17].

HE is a neurological syndrome caused by liver dysfunction and portosystemic shunting, leading to accumulation of neurotoxins, such as ammonia, that cross the blood-brain barrier and affect cerebral function [18]. Astrocytic swelling induced by ammonia, as well as oxidative stress, play key roles in the impairment of neuronal function, even though its pathogenesis is also induced by systemic inflammation and altered cerebral perfusion [19]. HE is widely associated

with impaired cognition, increased hospitalization, reduced autonomy and reduced quality of life [20]. It is clinically categorized into 2 stages: minimal HE (MHE), which is subclinical and can be diagnosed only through specialized psychometric testing, and overt HE (OHE), which is characterized by disorientation, lethargy or coma [21]. MHE is very common among patients with cirrhosis, and is associated with an increased risk of disease progression and mortality. In a large multicenter study, MHE diagnosed by psychometric HE score (PHES) was independently associated with a 74% higher risk of progression to OHE, as well as a 53% higher risk of liver transplantation or death [22]. In addition to its epidemiological importance, MHE constitutes a complex cerebral dysfunction characterized by subtle, yet widespread deficits in attention, psychomotor speed and executive control. These arise despite the absence of overt clinical signs, making it hard to detect them in routine clinical settings [23]. Cognitive alterations reflect underlying heterogeneous neurophysiological and functional disturbances, including altered sensory processing, impaired inhibitory responses and working memory disruptions, characterizing MHE as a multidimensional brain disorder, rather than a single-pathway complication of liver failure [24]. Since no single test adequately captures its underlying pathophysiology, the diagnosis of MHE remains methodologically challenging, supporting the need for more sensitive diagnostic tools [25].

Electroencephalography (EEG) allows objective evaluation of cortical network dysfunction, and in patients with cirrhosis it could provide important information for disease staging, diagnosis of MHE, and prognosis [26]. Considering the clinical importance of early detection and risk stratification, this review examines the current literature on the diagnostic and prognostic utility of EEG and its quantitative derivatives across the spectrum of HE.

EEG spectral analysis: metrics and clinical applications across brain disorders

EEG is a commonly used noninvasive method for recording voltage fluctuations from neuronal activity, providing real-time insights into cerebral function through high temporal resolution [27]. Traditionally, qualitative EEG interpretation was based on visual assessment of waveforms by neurologists, but this was subject to interobserver variability and had limited sensitivity [26].

In contrast, spectral analysis breaks down an EEG waveform into its constituent frequencies, using the Fast Fourier Transform (FFT) technique to convert varying voltage signals into a power spectrum, and enabling objective quantification of neural oscillations that cannot be easily distinguished through visual inspection [28,29]. This facilitates the recognition of pathological activity and allows efficient visualization of temporal trends. As a complement to spectral analysis, wavelet-based multichannel EEG analysis enables simultaneous time-frequency decomposition of non-stationary signals, allowing transient oscillatory dynamics and spatial patterns of cortical

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activity to be captured with higher sensitivity [30]. Spectral analysis can improve reproducibility, because it provides operator-independent numerical parameters, reducing dependence on interpreter expertise and thus minimizing interobserver variability.

Quantitative EEG (qEEG) frameworks expand FFT-based spectral analysis though extracting advanced metrics, such as band-power ratios, coherence measures and nonlinear complexity indices, capturing subtle alterations in neural network dynamics relevant to early cerebral dysfunction [31]. Specifically, spectral analysis enhances diagnostic accuracy by quantifying frequency components, such as delta, theta, alpha and beta waves, in a mathematically objective manner [32]. Ratios of frequency bands offer important information on cortical dynamic imbalances, such as increased slow-wave activity or reflected disruptions in neural synchronization, which characterize cognitive impairment and brain dysfunction [33]. A very useful index that complements single-frequency indices is mean dominant frequency (MDF). This quantifies the power of multiple spectral peaks, facilitating the characterization of frequency dispersion and providing a multidimensional view of cortical dysfunction that single-band measures alone cannot capture [34]. Critical flicker frequency (CFF) constitutes the threshold at which flickering light is perceived as continuous, an index of visual processing speed and cortical arousal, while its sensitivity to subtle cognitive impairment supports its use in conditions such as MHE [35]. Lastly, event-related potentials (ERPs), which measure components such as N200 (N2), an earlier negative deflection associated with stimulus processing, and P300, a later positive waveform reflecting attention and stimulus processing by coordinated frontal and temporal-parietal activity, could be used in conditions characterized by disrupted information processing, given their sensitivity to cognitive dysfunction [36]. The analytical workflow leading from routine EEG acquisition to spectral analysis markers such as MDF, and advanced signal decomposition with clinical and psychometric models for diagnostic and prognostic assessment, is illustrated in Fig. 1.

EEG spectral analysis has shown considerable diagnostic and prognostic value across neurological and psychiatric diseases, supporting its potential clinical utility in HE. In various diseases, including epilepsy, frequency-specific spectral measures were able to examine neural responses to neuromodulation therapies, allowing objective monitoring of treatment effects [37]. Spectral abnormalities can also be present in dementia, where decreased alpha power accompanied by increased delta–theta activity have been strongly associated with cognitive decline, supporting their possible use as biomarkers of neurodegeneration [38]. In metabolic encephalopathies, progressive slowing of EEG rhythms from the alpha to the theta and delta bands reflects the severity of cortical dysfunction, resulting in a graded indicator of metabolic cerebral dysfunction [39]. Research conducted in psychiatric patients has linked specific symptom domains to frequency-band disruptions, such as elevated theta and reduced alpha power, showing how oscillatory changes encode cognitive and emotional dysfunction [40]. Spectral

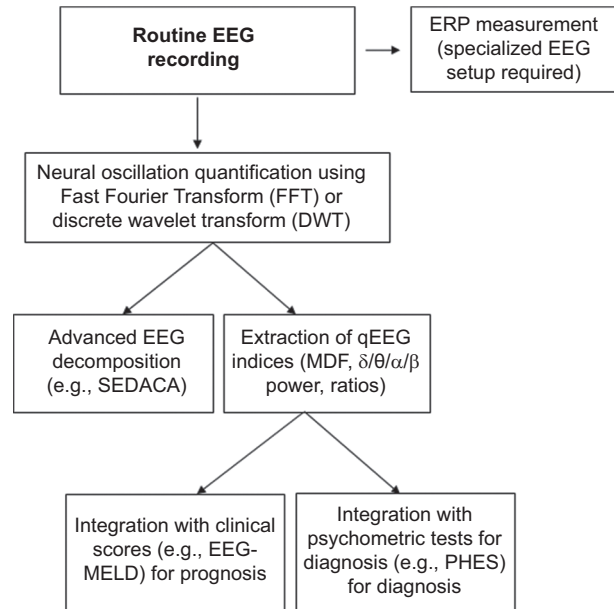


Figure 1 Workflow from EEG acquisition to diagnostic and prognostic modeling

EEG, electroencephalography; qEEG, quantitative electroencephalography; ERP, event-related potential; SEDACA, short-epoch dominant-activity cluster analysis; MDF, mean dominant frequency; PHES, psychometric hepatic encephalopathy score; MELD, model for end-stage liver disease

markers, such as gamma-band alterations, alpha asymmetry and power alterations, have been extensively investigated as possible biomarkers in various psychiatric diseases, including depression, bipolar disorder and schizophrenia, supporting their diagnostic and prognostic promise [41]. In amnesic mild cognitive impairment, qEEG reveals increased theta–delta power, reduced beta activity, and coherence disturbances—patterns that sensitively capture early cognitive decline [42]. These findings support the broad diagnostic and prognostic utility of EEG spectral analysis across diverse brain disorders, providing a strong rationale for exploring its potential role in HE, an evaluation undertaken in the following section.

EEG and ERP markers of cognitive and cortical dysfunction in cirrhosis

To provide an integrated overview of the neurophysiological disturbances observed in cirrhosis, this section summarizes the EEG- and ERP-based findings that characterize cognitive and cortical dysfunction across the full spectrum of HE. EEG spectral analysis has shown that reductions in MDF correlate significantly with poorer psychometric performance, and can independently predict cognitive impairment [43]. Abnormalities such as reduced MDF or increased slow-frequency power were present in a substantial proportion of cirrhotic patients, and were independently associated with impaired portal

flow, elevated ammonia levels and reduced prothrombin time [44]. Significant alterations in relative EEG power across the theta, delta, alpha and beta bands were observed in cirrhotic patients, particularly in those with Child-Pugh class C disease, while psychometric testing detected cognitive impairment in 48% of patients, and abnormalities in attention and processing tasks in up to 80%, supporting the value of EEG as an objective tool for detecting early neuropsychiatric alterations in cirrhosis [45]. Spectral EEG parameters were primarily influenced by cirrhosis itself, with alcoholic cirrhosis showing more pronounced slowing, demonstrating that EEG spectral abnormalities reliably reflect brain dysfunction, independently of confounders such as hepatitis C virus infection [46].

Complementing these spectral findings, spatiotemporal EEG decomposition (SEDACA) a method that separates EEG activity across brain regions and time, provided more accurate dominant-frequency estimates, and revealed a shift of the normally posterior background rhythm toward anterior regions, both of which correlated strongly with MHE and OHE and outperformed standard spectral analysis [47]. Oral amino acid-induced hyperammonemia produced significant EEG slowing, reflected by an increased slow/fast-wave ratio that correlated with rising ammonia levels, demonstrating a direct ammonia-linked neurophysiological deterioration [48]. In cirrhotic patients without OHE, EEG spectral analysis detected abnormalities more frequently (41%) than psychometric tests or P300 latency, and correlated more closely with liver function, demonstrating that qEEG adds diagnostic value while P300 provides minimal additional information [49].

ERPs also highlighted early cortical dysfunction, demonstrating significantly prolonged latency in cirrhotic patients without OHE, outperforming psychometric tests and confirming ERPs as a sensitive tool for detecting early neurocognitive dysfunction [50]. Further analysis revealed that N200 latency, not P300, was the earliest and most sensitive neurophysiologic abnormality in cirrhotic patients, indicating that slowed auditory cortical processing precedes classic cognitive deficits [51]. Psychometric testing has already demonstrated significant deficits in memory and processing speed, even in cirrhotic patients without OHE, reinforcing the hypothesis that early neurocognitive dysfunction can be consistently detectable before clinical manifestations [52]. These findings indicate that EEG and ERP techniques could be useful in the detection of early and progressive neural dysfunction in cirrhotic patients, with notable sensitivity, providing a reliable neurophysiological framework for monitoring HE.

Electrophysiological markers for the diagnosis of MHE

In order to examine how electrophysiological methods contribute to the diagnosis and prognosis of MHE, this section reviews the contributions of EEG, coherence, ERP, sleep and psychometric-based evidence to the assessment of early

neurocognitive impairment in cirrhosis. A comprehensive overview of all included studies investigating the utility of EEG in the diagnosis of MHE is presented in Table 1. EEG spectral analysis identified 34% of cirrhotic patients without OHE, showing that an increase in theta power (>35%) was correlated with liver dysfunction [53]. The studies included in this overview, as well as those summarized in subsequent sections examining the prognostic role of EEG in HE (Table 2), were identified through a targeted literature search of the PubMed and Scopus databases, supplemented by screening the reference lists of relevant articles. Eligible studies were those evaluating electroencephalographic parameters in cirrhotic patients in relation to MHE, cognitive impairment, or clinical outcomes.

Standard EEG in cirrhotic patients demonstrated diffuse slowing of background activity, where the severity of EEG abnormalities was correlated with both neuropsychological test performance and liver dysfunction [54]. Brain electrical activity mapping further revealed significant slowing of peak frequency, and increased theta and beta activity, even in cirrhotic patients without clinical symptoms, showing high sensitivity for detecting subclinical neuropsychiatric disturbances [55]. Spectral EEG detected neurophysiological abnormalities, defined by elevated theta power or reduced dominant frequency, in a subset of cirrhotic patients, with these abnormalities being more frequent in older individuals, those with higher ammonia levels, and those with more advanced liver disease [56]. However, it should be noted that spectral analysis in this study presented very poor agreement with psychometric tests in measuring disease severity [56], while the results from 2 additional studies [57,58] also demonstrated poor concordance. Those findings suggest that further research is required to clarify the diagnostic value of EEG in MHE compared to traditional methods.

Although the overlap between EEG abnormalities and psychometric test performance has been questioned, evidence summarized by Amodio *et al* supports the view that qEEG, and especially MDF, may still represent a useful parameter for the diagnosis of MHE [59]. Automated spectral EEG detected slowing in 19% of stable cirrhotic patients and, together with psychometric impairment, defined subclinical HE, independently predicting worse daily functioning in all domains of the Sickness Impact Profile questionnaire [57]. EEG coherence analysis revealed that cirrhotic patients showed increased theta coherence in frontal–central and frontal–occipital networks, together with reduced alpha-band coherence across several cortico–cortical pathways, indicating abnormal functional coupling of resting-state neural rhythms in cirrhosis [60]. Wavelet-based multichannel EEG analysis in cirrhotic patients revealed progressive slowing of cortical rhythms, characterized by increased delta ($33.3 \pm 16.6\%$ vs. $17.0 \pm 10.6\%$, $P=0.001$) and theta ($23.6 \pm 13.2\%$ vs. $13.7 \pm 6.0\%$, $P=0.001$) power, together with reduced alpha activity ($24.1 \pm 12.8\%$ vs. $51.7 \pm 18.2\%$, $P<0.001$) compared with healthy controls, while both spectral and dynamic EEG indices correlated significantly with PHES scores ($P<0.05$), supporting combined spectral–dynamic parameters as potential biomarkers of neurocognitive impairment [61]. Finally,

Table 1 Summary of studies evaluating the role of EEG in MHE

Study [ref.] (year)	Study design	Sample	Primary outcome	Secondary outcome
Amodio <i>et al</i> [53] (1996)	Cross-sectional	50	Reduced MDF and increased theta power in MHE patients	Quality EEG analysis fails to diagnose MHE
Amodio <i>et al</i> [43] (2003)	Cross-sectional	68	MDF as independent diagnostic marker psychometric scores	Lower MDF correlated with brain atrophy
Amodio <i>et al</i> [49] (2005)	Cross-sectional	86	MDF combined with psychometric tests improves diagnosis of MHE	Lower MDF correlated with higher Child-Pugh and increased bilirubin
Amodio <i>et al</i> [67] (2006)	Cross-sectional with prospective follow up	238	Reduced MDF correlated with lower mZPS	EEG abnormalities correlated with Child-Pugh, lower albumin and increased bilirubin
Campagna <i>et al</i> [46] (2014)	Cross-sectional	90	MDF combined with MZPT improve diagnosis of MHE	EEG and psychometrics differ based on cause of disease
Groeneweg <i>et al</i> [57] (1998)	Cross-sectional	179	Poor agreement between EEG abnormalities and psychometric tests in MHE patients	EEG abnormalities correlated with Child-Pugh
Jackson <i>et al</i> [73] (2016)	Cross-sectional	226	SEDACA-derived reduced MDF and increased theta power in MHE patients	Conventional spectral EEG analysis fails to diagnose MHE
Johansson <i>et al</i> [64] (1989)	Cross-sectional	42	Spectral EEG indices correlated significantly with PHES	Spectral EEG indices not correlated with Child-Pugh and MELD
Koziarska <i>et al</i> [62] (2013)	Prospective cross-sectional	101	MDF not correlated with MMSE score	Reduced MDF correlated with Child-Pugh and West Haven but not MELD
Kullmann <i>et al</i> [55] (2001)	Cross-sectional	48	Lower peak frequency and elevated beta bands in patients with normal psychometric tests	EEG abnormalities correlated with Child-Pugh
Marchetti <i>et al</i> [68] (2011)	Prospective observational cohort	175	Reduced MDF correlated with lower mZPS	EEG abnormalities correlated with Child-Pugh, lower albumin and increased ammonia
Maric <i>et al</i> [54] (2011)	Case-control observational	60	EEG abnormalities in MHE patients	EEG abnormalities correlated with Child-Pugh
Mohamed <i>et al</i> [45] (2024)	Cross-sectional	50	MDF combined with psychometric tests improve diagnosis of MHE	EEG abnormalities correlated with Child-Pugh
Montagnese <i>et al</i> [47] (2007)	Cross-sectional	110	SEDACA distinguish MHE patients from control	MDP showed progressive anteriorization of the PBR through disease stages
Moon <i>et al</i> [51] (2014)	Cross-sectional	50	ERPs N200 and P300 delayed in MHE patients	N200 latency is abnormal even when PHES and P300 are normal
Pascoli <i>et al</i> [74] (2006)	Cross-sectional	61	Novel time-domain indices correlated with psychometric scores in MHE patients	EEG abnormalities correlated with Child-Pugh
Quero <i>et al</i> [56] (1996)	Cross-sectional	137	Poor agreement between EEG abnormalities and psychometric tests in MHE patients	EEG abnormalities correlated with Child-Pugh and increased ammonia levels
Saxena <i>et al</i> [63] (2002)	Prospective observational cohort	75	Increased theta power and reduced alpha power in MHE patients	EEG abnormalities correlated with Child-Pugh
Schiff <i>et al</i> [75] (2016)	Cross-sectional/validation	72	Reduced MDF and increased theta power in MHE patients	Reduced MDF correlated with higher MELD
Wunsch <i>et al</i> [58] (2013)	Prospective cross-sectional	50	Poor agreement between EEG abnormalities and psychometric tests in MHE patients	Higher MDF correlated with higher PHES

MDF, mean dominant frequency; MHE, minimal hepatic encephalopathy; EEG, electroencephalography; mZPS, mean psychometric score; MZPT, mean Z score of psychometric tests; SEDACA, short-epoch dominant-activity cluster analysis; PHES, psychometric hepatic encephalopathy score; MELD, model for end-stage liver disease; MMSE, mini-mental state examination; MDP, mean dominant position; PBR, posterior basic rhythm; ERP, event-related potential

qEEG analysis revealed that reduced MDF was significantly associated with both MHE and OHE, whereas Mini-Mental

State Examination scores failed to distinguish MHE from unimpaired patients [62].

Table 2 Summary of studies evaluating the prognostic role of EEG in HE

Study [ref.] (year)	Study design	Sample (n)	Follow up mean (days)	Primary outcome	Secondary outcome
Amodio <i>et al</i> [77] (2001)	Prospective cohort	296	442	qEEG predicted survival rates and OHE development, even after adjustment for Child–Pugh	EEG abnormalities correlated with Child–Pugh
Amodio <i>et al</i> [67] (2006)	Cross-sectional with prospective follow up	238	331	EEG abnormalities predicted survival rates and OHE development	EEG abnormalities correlated with Child–Pugh, lower albumin and higher bilirubin
Amodio <i>et al</i> [78] (2009)	Retrospective cohort	201	250	Higher theta power and alpha relative power predicted survival rates and OHE development	MDF and theta power correlated with Child–Pugh
Ficker <i>et al</i> [70] (1997)	Retrospective cohort	18	N/A	Epileptiform EEG abnormalities correlated with lower survival rates	Epileptiform EEG abnormalities are uncommon among HE patients
Koul <i>et al</i> [76] (2020)	Retrospective cohort	151	28	EEG grading predicted survival rates in ICU HE patients	Normal or improving EEG grading predicted higher survival rates in ICU HE patients
Marchetti <i>et al</i> [68] (2011)	Observational cohort with follow up	175	365	Lower MDF and higher theta power predicted survival rates and OHE development within 1 year	EEG abnormalities correlated with Child–Pugh, lower albumin and higher ammonia
Montagnese <i>et al</i> [81] (2014)	Observational cohort with follow up	392	365	Lower MDF predicted survival rates	Combined MELD-EEG had greater predictive value for 12- and 18-month survival rates than MELD alone
Stewart <i>et al</i> [72] (2014)	Prospective exploratory	20	74	Total WSE correlated with survival rates or liver transplantation in ICU patients with ALF	MDF and theta power are useful for grading HE, but not for predicting outcomes in ICU patients with ALF
Van der Rijt <i>et al</i> [65] (1985)	Retrospective cohort	70	1080	High-grade EEG abnormalities predicted very high short-term mortality risk	Low-grade EEG abnormalities predict preserved survival rates

qEEG, quality electroencephalography; OHE, overt hepatic encephalopathy; EEG, electroencephalography; MDF, mean dominant frequency; HE, hepatic encephalopathy; ICU, intensive care unit; MELD, model for end-stage liver disease; WSE, wavelet sub-band entropy; ALF, acute liver failure

Studies examining ERPs further highlighted early cortical processing delays. In a study that compared patients in various disease stages with healthy control groups, cirrhotic patients with MHE showed markedly prolonged P300 latencies and reduced amplitudes, confirming delayed cognitive processing as a valuable neurophysiological marker of early encephalopathy [63]. Visual evoked potential testing in 42 cirrhotic patients demonstrated significant prolongation of cortical response latencies, with P2 and N3 peaks occurring 11% and 26% later than in healthy controls ($P < 0.01$ – 0.001). On the other hand, only 29% of patients exhibited clearly abnormal values, highlighting the considerable overlap with normal ranges and the superior sensitivity of psychometric testing for detecting HE. [64]. These findings indicate that spectral analysis, as discussed above, should be interpreted as complementary, rather than alternative tools to psychometric testing in MHE, while their imperfect concordance with psychometric scores underscores that EEG and cognitive tests probe partially distinct dimensions of cirrhosis-related brain dysfunction and are most informative when integrated within a multimodal diagnostic framework, rather than being used in isolation.

EEG predictors of OHE

Table 2 summarizes all the identified studies that evaluated the prognostic value of EEG in HE. Automated spectral EEG grading showed a strong inverse relationship between encephalopathy severity and survival, especially in grades 3–4 HE, establishing qEEG as a prognostic indicator in cirrhosis [65]. EEG abnormalities, as previously described, were closely associated with psychometric impairment in cirrhotic patients [66], while spectral EEG classification showed significant associations with liver disease severity, and independently predicted both mortality and the development of OHE [67]. Its prognostic performance proved comparable to both traditional visual EEG grading and the artificial neural network–expert system (ANNES), with spectral EEG parameters independently predicting survival in cirrhotic patients (hazard ratio 1.55, 95% confidence interval 1.15–2.09, $P = 0.004$), while providing a more objective and standardized assessment than conventional visual interpretation [67]. Reduced posterior MDF and increased parietal theta coherence were strongly associated with cirrhosis severity and elevated ammonia levels, independently predicting both 1-year

mortality and the development of OHE [68]. Additionally, an automated EEG classification system using neural networks accurately staged HE, and correlated strongly with Child-Pugh severity and biochemical liver dysfunction, offering an objective alternative to expert visual EEG grading, despite overestimating mild abnormalities [69].

Epileptiform EEG abnormalities, although present in only a minority of affected patients, are strongly associated with severe HE and markedly worse survival, highlighting the clinical relevance of seizure-related patterns in advanced disease [70]. Classical descriptions of HE emphasize the appearance of triphasic waves, demonstrating that triphasic activity in portal-systemic encephalopathy can be reliably enhanced by photic stimulation or bemegride, supporting a shared mechanistic basis with other generalized synchronizing EEG patterns [71]. In acute liver failure, abbreviated qEEG—particularly reductions in spectral edge frequency and increased delta power—accurately tracks HE stage, while wavelet entropy predicts death or need for transplantation more reliably than transcranial Doppler pulsatility, supporting qEEG as a practical tool for HE monitoring in the intensive care unit, and for prognostication [72]. EEG spectral indices, particularly reduced MDF and increased theta power, showed systematic changes across unimpaired, MHE and OHE groups, and newly derived spectral thresholds significantly improved diagnostic performance compared with conventional criteria [73]. Methodological optimization of spectral EEG reveals that low-frequency noise and epoch length critically influence stability, while novel time-domain indices show stronger associations with psychometric performance than do traditional spectral measures, suggesting better sensitivity to cognitive dysfunction [74]. In a cohort of 72 cirrhotic patients, portable wireless EEG produced automated spectral parameters that closely matched those obtained with standard EEG ($r=0.41-0.83$, $P<0.001$) and demonstrated good diagnostic agreement, while the MDF derived from the device correlated significantly with MELD ($r=-0.39$), venous ammonia levels ($r=-0.41$) and PHES performance ($r=0.49$), confirming that clinically meaningful qEEG slowing can be reliably captured using inexpensive, user-friendly systems suitable for routine assessment [75].

Additional neurophysiological modalities corroborate these findings. EEG severity grading demonstrated a strong association with clinical outcome, showing markedly higher mortality in patients who exhibited grade 3-4 patterns, including frequent triphasic waves and periodic discharges, and supporting the prognostic value of EEG in hospitalized HE patients [76]. Reduced MDF and elevated slow-wave power have been correlated with liver disease severity, ammonia levels and prior overt episodes, and independently could predict both future OHE and liver-related mortality [77]. When FFT is compared with autoregressive spectral techniques, both methods show similar correlations with ammonia, clinical severity and prognosis; however, autoregressive modelling provides smoother and more stable estimates, particularly for low-power bands, and requires fewer epochs to obtain reliable values [78]. Finally, magnetoencephalography reveals slowed somatosensory alpha peak frequency, delayed

rebound and blunted cortical re-engagement with increasing HE severity, changes that correlate with critical flicker frequency, Child-Pugh class and ammonia, thereby capturing impairments in oscillatory sensory processing beyond global EEG slowing [79].

The MELD score has long been established as the cornerstone for assessing disease severity and guiding transplant allocation in advanced liver disease. However, because it is derived exclusively from laboratory markers of hepatic and renal dysfunction, it does not directly reflect cerebral involvement or quantify the prognostic impact of HE [80]. Integration of MDF into the MELD-EEG index significantly improves mortality prediction, increases sensitivity, reduces misclassification and lowers unnecessary transplant allocation, confirming the additive prognostic utility of automated qEEG markers [81]. This integrated prognostic model offers a realistic example of how EEG could be incorporated into everyday clinical practice, with the automated and operator-independent assessment of MDF allowing neurophysiological dysfunction to be quantified into the MELD score. Taken together, automated qEEG markers, and especially MDF, could be used as complementary parameters to traditional scores, allowing for a more comprehensive and reproducible clinically actionable stratification of risk in HE patients.

Discussion

The aim of this review is to provide an integrated and balanced synthesis of the available evidence in the literature concerning the role of EEG in disease diagnosis and prognosis across different stages of HE. Integrated findings from traditional EEG, coherence and functional connectivity analyses, spectral methods, ERP measurements and automated machine-learning approaches were examined, with a view to bringing together complementary research approaches that are frequently studied alone. The principal finding that emerges from this review is that EEG can capture meaningful, measurable alterations in cortical function throughout the different stages of cirrhosis, including MHE. These abnormalities, though heterogeneous among studies, show that liver dysfunction is consistently reflected in neural networks, which thus contain potential diagnostic and prognostic clinical information that requires further exploration.

One of the most important challenges in the clinical management of cirrhosis is the early detection of MHE. Although it may present subtly, MHE is associated with a reduced quality of life, functional impairment, a greater risk of driving accidents, and a significantly higher probability of progressing to OHE and mortality [82]. Commonly used psychometric tools, such as PHES, show important limitations, including cultural dependence, learning effects, interobserver variability and partial capture of neurophysiological dysfunction, underscoring the need for additional diagnostic tools [83]. Given this context, EEG can be considered an objective, physiology-based evaluation of brain function, with direct implications for prognosis, timely management

and prevention of clinical deterioration. Multiple studies have shown that qEEG parameters, especially lower MDF, increased theta and delta power, and altered spectral ratios, are associated with liver disease severity, ammonia levels and portal hypertension. This suggests that qEEG slowing reflects a downstream expression of metabolic and neurotransmitter disturbances, consistent with known mechanisms such as astrocytic swelling, glutamatergic dysfunction and impaired cortical–subcortical communication [55,68,84].

The current literature does not provide a uniformly consistent picture. Some studies found only poor agreement between EEG spectral measures and psychometric tests, raising the possibility that each modality captures different dimensions of cognitive dysfunction [57,58]. This divergence may underscore the heterogeneity of MHE itself, and the difficulty of finding a single gold standard for its diagnosis. A multimodal approach, combining both psychometrics and EEG, perhaps even with potentially additional information from neuroimaging, could ultimately provide the most consistent assessment. Nonetheless, the ability of EEG to detect abnormalities independent of psychometric performance continues to be clinically important, especially in patients where psychometric testing is impractical or unavailable in routine practice.

One important issue in the examined literature concerns connectivity-based and dynamic EEG analyses. Increased theta coherence in frontal–central and frontal–occipital networks, with reduced alpha coherence across widespread cortical regions, has been described by various studies, even in the absence of overt symptoms [43]. These observations suggest that, beyond generalized slowing, cirrhosis also disrupts the interaction between neural oscillators, potentially reflecting altered thalamocortical communication or impaired large-scale network integration. Similarly, wavelet-based and multichannel approaches have detected rhythm anteriorization, progressive slowing and increased temporal variability, providing a more nuanced characterization of neural dysfunction that may complement standard spectral analysis [47,72]. ERPs could provide a useful viewpoint by measuring attention and processing speed. Prolonged N200 and P300 latencies in patients indicate early disruptions in sensory discrimination and higher-order cognitive evaluation long before OHE emerges [51]. ERP abnormalities were even detectable on the resting-state EEG while psychometric testing was still within normal limits, supporting the idea that ERPs could possibly be used to identify even earlier or more subtle cortical changes. It should be mentioned, however, that the use of ERPs is critically dependent on standardized stimulation paradigms and specialized equipment, which has limited their widespread adoption.

The clinical relevance of EEG in cirrhosis concerns not only diagnosis, but mostly its ability to predict disease progression and mortality. Reduced MDF, elevated slow-wave power and higher qEEG encephalopathy grades independently predicted the development of OHE, hospitalization and mortality in many studies [65,67]. Furthermore, there were cases in which EEG parameters provided prognostic information comparable

or additional to traditional clinical scores such as MELD and Child–Pugh [77,81]. This observation is clinically important, because current prognostic models rely heavily on biochemical markers and do not incorporate direct assessments of cerebral function. EEG-based markers could offer a complementary dimension that strengthens existing risk stratification approaches in cirrhosis, especially when we consider that neurological deterioration is a major cause of hospitalization and mortality. The integration of EEG metrics into integrated indices, such as the MELD-EEG, further supports its potential. Studies evaluating such models showed better sensitivity for mortality prognosis and less diagnostic misclassification, suggesting that even a single EEG parameter, when appropriately quantified, might improve prognostic accuracy [81]. Besides prognosis, spectral analysis can meaningfully contribute to clinical decision-making, by offering an objective, quantifiable assessment of cerebral dysfunction that can identify patients with increased risk for progression to OHE, even in the absence of overt neurological signs, thereby supporting earlier closer monitoring and prioritization for inpatient management in high-risk patients. Longitudinal evaluation of EEG spectral markers, especially changes in dominant frequency and slow-wave power, could provide a sensitive tool for monitoring treatment efficacy. Clinicians could use EEG markers to assess response to therapies such as lactulose or rifaximin, thus individualizing treatment strategies based on real-time neurophysiological feedback, rather than clinical observation alone.

Advances in automated EEG analysis and portable EEG devices represent another important development. Machine-learning models indicate the ability of new methods to classify HE stage with high accuracy and consistency, thus helping to address concerns regarding operator dependence and interpretive variability [85]. Portable wireless EEG systems, and the use of spectral metrics similar to those of standard laboratory EEG, could allow for bedside or outpatient screening and follow-up [75]. These innovations could lower the practical and financial barriers to implementation, and could enable larger prospective studies needed to validate EEG biomarkers across heterogeneous clinical settings. Within this framework, while further evidence from prospective studies accumulates, portable EEG platforms could be implemented on a pilot basis in transplantation centers, as complementary tools to traditional clinical severity scores such as MELD or MELD-Na, offering objective neurophysiological information that could help identify patients with early cerebral dysfunction.

An important distinction must be made between EEG-based methods that require specialized neurophysiology laboratories and highly trained personnel—such as source localization, ERPs and advanced functional connectivity analyses—and methods that can be calculated from standard or even simplified EEG recordings, including qEEG, MDF and ratios. Whereas the former provide in-depth pathophysiological insight into cortical processing and network-level dysfunction, their cost, complexity, long acquisition times, and in particular the need for expert interpretation, constrain their broader implementation outside specialized referral centers. In comparison, spectral EEG measures obtained from routine

recordings or portable devices provide a practical balance between physiological relevance and feasibility, as they can be quickly obtained, automated and interpreted, with minimal operator dependency. Crucially, the integration of modern signal-processing methods, cloud-based analytics and artificial intelligence-driven models has the potential to reduce overall cost, shorten analysis time, and simplify training requirements, thereby supporting wider implementation of EEG-based tools for risk stratification and monitoring in cirrhosis across diverse healthcare settings.

Alongside EEG, blood-based biomarkers measuring ammonia metabolism, systemic inflammation and central nervous system injury have shown possible clinical relevance in the diagnosis and prognosis of HE [86]. Evidence from a recent systematic review and meta-analysis suggest that deviations in ammonia and routine laboratory and inflammatory parameters are consistently associated with HE, suggesting their possible integrative role [87]. Compared with traditional tools, the prospective evaluation of brain-derived serum biomarkers, such as S-100 β , has shown a more variable association with disease severity scores and treatment response, suggesting that these biomarkers' greatest clinical value may emerge when they are integrated with functional assessments such as EEG, rather than used in isolation [88].

Although these findings are promising, EEG usage presents important limitations. Methodological heterogeneity across studies—different electrode montages and artifact handling, and deviations in recording conditions, spectral algorithms and diagnostic thresholds—limits their direct comparability. This variability is highlighted by the need for standardized protocols to allow reproducibility and cross-center comparison. Another concern is that, even though EEG abnormalities are common in cirrhosis, they are not entirely specific to HE. Comorbidities such as metabolic disturbances, sleep deprivation, psychiatric medications and alcohol consumption may influence EEG patterns [89]. Well-designed studies with standardized exclusion criteria are needed to determine the specificity of EEG markers. The clinical usefulness of EEG relative to its practical demands also constitutes a serious concern. Standard EEG depends on specialized equipment, trained personnel and time for acquisition and interpretation. Portable and automated systems could reduce some of these limitations, but their broader implementation will depend on cost, usability, and integration into existing clinical workflows [90]. The value of EEG will be fully leveraged, not by replacing psychometric or biochemical assessments, but by complementing them within a novel multimodal diagnostic framework. Developing this argument further, our findings indicate that EEG spectral analysis, particularly objective measures such as MDF and quantitative power distributions, could be used as a complementary tool to psychomotor and psychometric tests, providing an independent neurophysiological assessment that enhances the diagnosis, risk stratification and longitudinal follow-up of HE, without displacing established cognitive assessment methods.

The evidence examined above indicates that EEG could provide a meaningful and physiologically grounded tool to assess brain dysfunction in cirrhosis. Its ability to detect

subclinical changes, monitor disease progression and predict clinical outcomes makes it a potentially valuable method for enhancing early detection and refining prognosis in both MHE and OHE. The field would benefit from larger, well-designed prospective studies using EEG protocols and integrating modern analytical techniques. Such investigation could help clarify the diagnostic accuracy of EEG markers, illuminate their relationship to psychometric and imaging-based methods, and define their practical role in routine clinical care.

In summary, EEG appears promising as a supplementary biomarker that may complement traditional techniques for assessing HE. While additional validation is needed, the emerging evidence supports the cautious but optimistic view that EEG could contribute to earlier detection, more accurate risk stratification, and potentially better outcomes for patients with cirrhosis, particularly in light of recent advances in artificial intelligence. Further research incorporating electrophysiological measures with clinical, biochemical and neurocognitive markers will play a central role in translating these findings into meaningful clinical practice.

Concluding remarks

HE remains an important clinical challenge in the management of cirrhosis, particularly in its covert stage, MHE, which often escapes detection despite carrying substantial functional and prognostic importance. EEG is able to capture consistent and reproducible patterns of cortical dysfunction that correlate with cognitive impairment, biochemical disturbances and liver disease severity. By enabling an objective, physiology-based assessment of cerebral involvement, EEG adds a neurophysiological dimension that serves as a complement to psychometric testing and biochemical scoring systems. Quantitative parameters, such as MDF, slow-wave power, spectral ratios, coherence alterations and advanced EEG grading systems, have repeatedly been observed as independent predictors of OHE, hospitalization and mortality. The incorporation of EEG markers in integrated prognostic models, such as the MELD-EEG index, improves risk stratification, complementing traditional laboratory-based scores by providing a direct measure of cerebral dysfunction. Future studies should emphasize methodological standardization, as well as the integration of EEG with other biomarkers, such as biochemical measurements and imaging, to establish reliable multidimensional assessment models for HE. Following continued refinement, EEG-based methods could contribute to earlier diagnosis, better monitoring of disease progression, and possibly better clinical outcomes for patients living with cirrhosis.

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