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Original Article

Bibliometric and Visualization Analysis of Hepatic Encephalopathy Research (2000-2024): Trends, Collaborations, and Future Directions

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Abstract:

Background: Hepatic encephalopathy (HE) is a neuropsychiatric disorder resulting from severe liver dysfunction or portosystemic shunting. It carries high morbidity and mortality and imposes a substantial burden on healthcare systems. This study aims to map the knowledge structure, highlight research hotspots, reveal emerging trends, and propose future directions in the field using bibliometric and visualization analysis.

Methods: A comprehensive search was conducted in the Web of Science Core Collection (SCI-EXPANDED and CPCI-S) to identify literature on hepatic encephalopathy published between 2000 and 2024. Quantitative and visual analyses were performed using VOSviewer and CiteSpace software to examine patterns of authorship, institutional contributions, journal dissemination, geographic distribution, keyword co-occurrence, co-authorship, citations, and co-citations, with the aim of objectively presenting and forecasting research trends in the field.

Results: A total of 8,723 relevant publications were identified. The number of annual publications has steadily increased over the years. Network analyses revealed that the United States, the journal *Metabolic Brain Disease*, and author Jasmohan S. Bajaj were the most influential contributors in terms of national output, institutional productivity, and individual authorship, respectively. Spain exhibited the highest average citation count per publication, reflecting notable academic impact. Reference co-citation and keyword co-occurrence analyses highlighted emerging research frontiers, including "risk," "mortality risk," "American Association" (referring to AASLD/EASL guidelines), "sarcopenia," and "decompensated cirrhosis" as sustained thematic focuses.

Conclusion: Research on hepatic encephalopathy has expanded considerably over the past two decades. Current studies predominantly focus on risk stratification, treatment efficacy, and underlying mechanisms. There is a discernible trend toward multidisciplinary integration, encompassing microbiome science, nutritional assessment, neuroimaging, and artificial intelligence. Among these, risk assessment is poised to remain a central focus in guiding future research and clinical management of hepatic encephalopathy.

Keywords：hepatic encephalopathy；risk；Nutritional guidelines

1. Introduction

Hepatic encephalopathy (HE) is characterized by a spectrum of motor, sensory, and cognitive impairments of variable severity[1-3]. Although many of the neurological symptoms are reversible following resolution of an HE episode, residual cognitive deficits often persist[4]. Epidemiologically, HE represents a common and serious complication in patients with advanced

liver disease—affecting approximately 10% of individuals with compensated cirrhosis, up to 20% of those with decompensated cirrhosis, and nearly 50% of patients who have undergone transjugular intrahepatic portosystemic shunt (TIPS) placement[5]. Furthermore, the annual recurrence rate of HE following an initial episode is as high as 50%[6]. HE is also the leading cause of hospital readmission in patients with cirrhosis[7]. Beyond its clinical burden, HE markedly impairs health-related quality of life and functional independence in both patients and caregivers, and current standard-of-care therapies provide only limited efficacy[8,9]. An in-depth understanding of emerging research trends, pathogenic mechanisms, and key risk factors in hepatic encephalopathy is essential for enabling timely interventions and preventing serious complications. Given the substantial clinical burden of HE and the limitations of current therapeutic approaches, a comprehensive evaluation of the evolving research landscape is vital for informing future investigative directions. Bibliometric analysis provides an effective and objective methodology for accomplishing this goal.

Bibliometric analysis is a quantitative method used to evaluate and visualize the structure, dynamics, and emerging trends within a specific research domain. By statistically analyzing published literature, it enables the identification of research hotspots, thematic frontiers, and influential contributors—including countries, institutions, and individual authors. This approach provides clinicians and researchers with a comprehensive and transparent overview of the current development status of a field, serving as a valuable guide for future investigations. In the context of hepatic encephalopathy, which contributes to substantial impairment in daily functioning, increased hospitalization rates, and diminished quality of life, bibliometric analysis can yield critical insights[10]. Compared to other complications of chronic liver disease, HE imposes a particularly complex burden on both patients and healthcare systems[11]. This study, therefore, employs bibliometric techniques to map the existing knowledge base, identify key themes, and forecast future research directions in hepatic encephalopathy.

Material and Methods:

1. Data Retrieval Strategy, Data Extraction, and Cleaning

The objective of this study was to conduct a comprehensive bibliometric analysis of research on hepatic encephalopathy. The Web of Science Core Collection, recognized as one of the most authoritative and comprehensive databases, was selected as the primary data source. Specifically, the Science Citation Index Expanded (SCI-EXPANDED) and the Conference Proceedings Citation Index - Science (CPCI-S) were queried using the advanced search term: TS = ("hepatic encephalopathy"). The search period covered the years 2000 to 2024, yielding an initial total of 12,201 records. After excluding non-English articles, conference abstracts, letters, editorials, and duplicates, a manual screening of titles, abstracts, and keywords was conducted to remove irrelevant studies. The final dataset included 8,723 publications. The literature selection and screening process is illustrated in Figure 1 (PRISMA flow diagram).

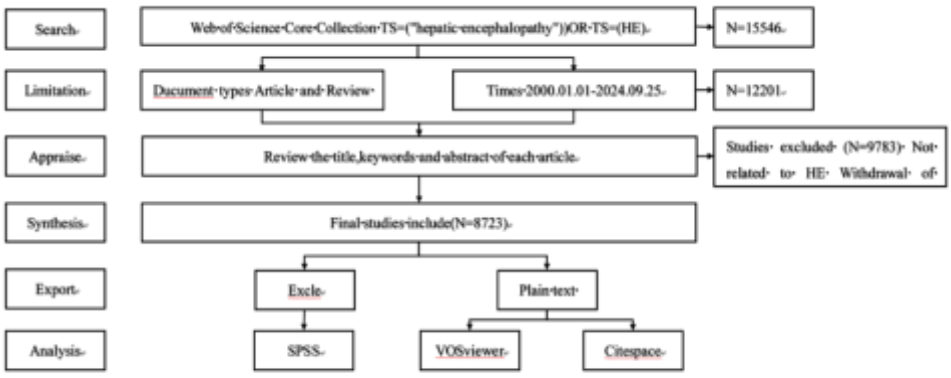

Figure 1. Literature screening flowchart

2. Scientometric Analysis Methods

The retrieved dataset of 8,723 publications was exported in plain text format for analysis. Microsoft Excel 2019, VOSviewer, and CiteSpace were employed to perform a series of scientometric and visualization tasks. These included overall publication trend analysis, synonym normalization, frequency analyses by country/region, institution, author, and funding agency, as well as keyword co-occurrence clustering. Additionally, co-occurrence and dissimilarity matrices, bimodal network overlays, and burst keyword detection were utilized to identify major research hotspots and emerging frontiers within the field of hepatic encephalopathy.

3. Results

3.1 Global Publication Trend

Between 2000 and 2024, the Web of Science (WoS) database identified a total of 8,723 publications related to hepatic encephalopathy. The annual number of publications has shown a consistent upward trajectory since 2000, reaching a peak of over 600 articles in 2023 (Figure 2). This trend reflects a sustained and growing interest in the field, suggesting that hepatic encephalopathy remains an emerging and evolving research focus within hepatology.

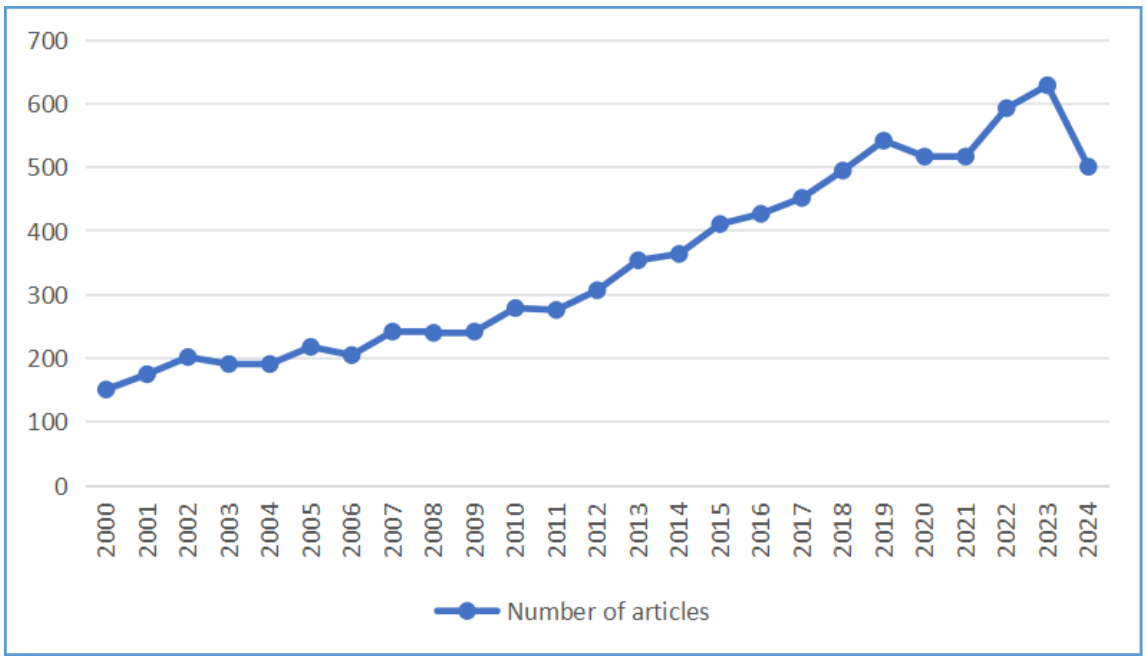

Figure 2. Annual publication trend on hepatic encephalopathy research, 2000-2024

3.2 Distribution of Countries, Institutions, and Journals

A total of 119 countries have contributed to research on hepatic encephalopathy. Among them, the United States was the most prolific, accounting for 1,950 publications (22.4% of all articles), followed by China (1,148 publications, 13.2%), Japan (561, 6.4%), Spain (537, 6.2%), and India (525, 6.0%).

Further analysis of research impact among the top five countries revealed that the United States, while leading in total publication volume, also achieved high citation counts and academic influence, positioning it as the global leader in hepatic encephalopathy research (Figure 3). Notably, although Spain, India, and Japan produced fewer articles than China, they demonstrated higher average citations per article. Spain, despite a relatively modest publication volume, exhibited the highest average citations per paper—significantly surpassing both the United States and China—indicating longstanding research strengths and substantial academic influence in the field.

In contrast, while China has experienced rapid progress in medical research in recent years and ranks second in total publications, its articles are characterized by lower citation counts and academic impact. This may be partially attributed

to limited international collaboration. As shown in Figure 4, we analyzed international collaboration among countries with more than 20 publications. In this network, node size represents publication volume, while the thickness of connecting lines reflects the strength of collaborative ties. The United States and Spain demonstrated strong global partnerships, whereas Chinese institutions appeared relatively isolated. This lack of collaboration may contribute to the lower quality and visibility of Chinese publications.

To enhance its global research presence, China is encouraged to increase investment in scientific resources, adopt advanced methodologies from developed countries, foster international partnerships, and promote domestic academic development.

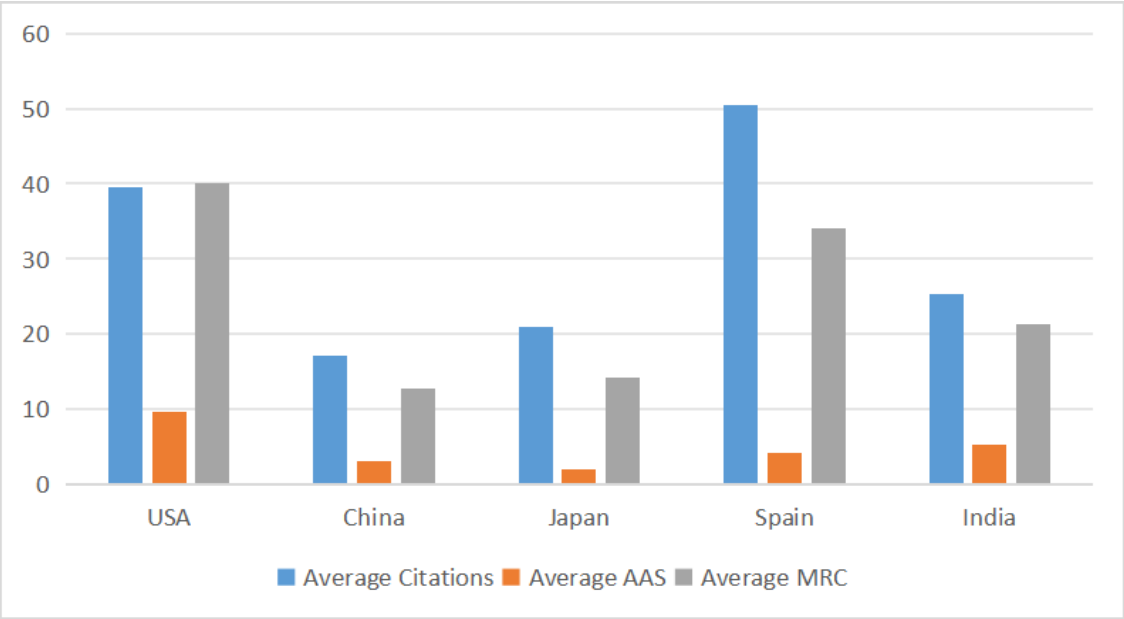

Figure 3. Comparison of national academic impact in hepatic encephalopathy research: mean number of citations, AAS(Average Article Score) and MRC(Mean Relative Citation Rate) analysis.

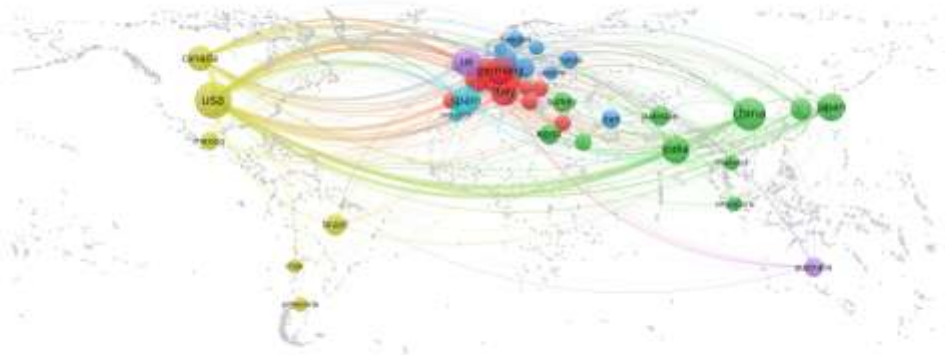

Figure 4. Collaboration network among countries/regions in hepatic encephalopathy research.

In total, 345 institutions with more than five publications on hepatic encephalopathy were identified. Table 1 lists the top ten journals by number of publications. *Metabolic Brain Disease* led with 312 articles (3.58% of total publications),

followed by the *Journal of Hepatology* (187, 2.14%), *Hepatology* (185, 2.12%), *World Journal of Gastroenterology* (183, 2.10%), and *Liver International* (166, 1.90%).

Co-citation analysis using VOSviewer and CiteSpace was used to determine total link strength, reflecting the centrality and interconnectedness of journals in the citation network. Among the top 10 journals, the *Journal of Hepatology* exhibited the highest total link strength (498,027), followed by *Hepatology* (342,986), *Liver International* (288,953), and *World Journal of Gastroenterology* (240,996). Notably, the *Journal of Hepatology* also had the highest Journal Impact Factor (JIF) at 26.8, followed by *Hepatology* (13.0) and *The American Journal of Gastroenterology* (7.98). JIF serves as a key metric for evaluating the academic influence and average citation performance of journals over a two-year period.

To explore the citation relationships and intellectual foundations of the field, a dual-map overlay of citing and cited journals was generated using CiteSpace (Figure 5). The left panel of the map represents citing journals—indicative of current research frontiers—while the right panel represents cited journals—comprising the knowledge base of the field. The connecting curves between these sets illustrate macro-structural patterns of scholarly development, including convergence, divergence, and cross-disciplinary integration. The resulting overlay suggests that hepatic encephalopathy research exhibits a highly interdisciplinary and intersecting development trajectory.

Table 1.Top 10 Source Journals in Hepatic Encephalopathy Research: Publication Output, Citations, and Impact.

Source	n^1	n^2	n^3	n^4
METABOLIC BRAIN DISEASE	312	9219	498027	3.2
JOURNAL OF HEPATOLOGY	187	21307	342986	26.8
HEPATOLOGY	185	26191	288953	13.0
WORLD J GASTROENTERO	183	5364	240996	4.3
LIVER INTERNATIONAL	166	5766	244297	6.0
HEPATOLOGY RESEARCH	133	2409	145508	3.9
EUR J GASTROENTEROL HEPATOL	131	2814	174842	2.3
DIGEST DIS SCI	118	3161	114534	2.5
J GASTROEN HEPATOL	114	3990	148458	3.7
AM J GASTROENTEROL	111	6942	198640	7.98

n^1: Number of documents published in the journal;
n^2: Total citations received by articles in this journal;
n^3: Total link strength (reflecting citation network centrality);
n^4: Journal Impact Factor (JIF).

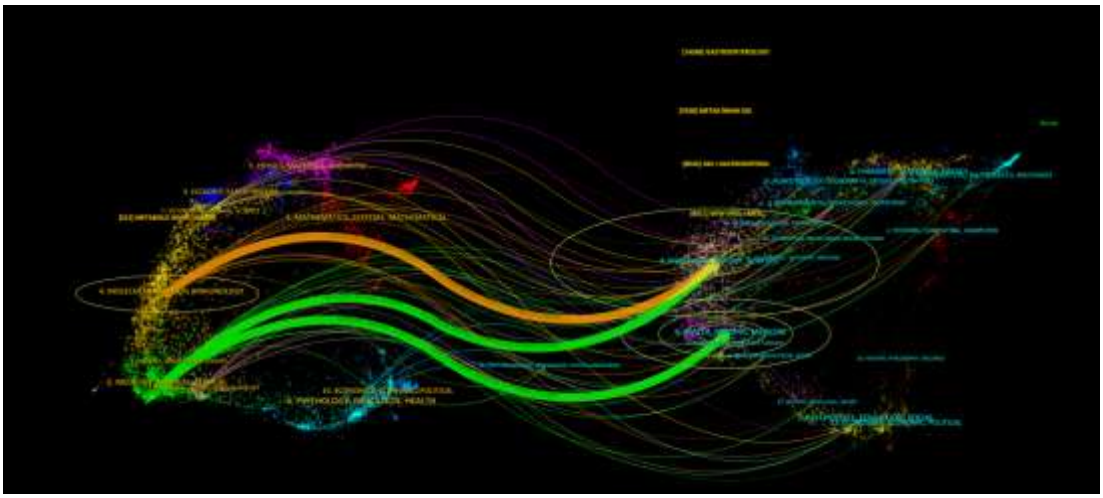

Figure 5. Dual-map overlay of journals citing and cited in hepatic encephalopathy research.

3.3 Authors

Over the past two decades, a total of 36,291 authors have contributed to more than 25 publications in the field of hepatic encephalopathy. Figure 6 presents a network map illustrating the collaborative relationships among these authors. Table 2 lists the top 10 authors ranked by publication count and citation frequency. Among them, Jasmohan S. Bajaj stands out as the most prolific and influential author, with a total of 10,885 citations. His significant contributions have played a pivotal role in shaping the direction and development of hepatic encephalopathy research, making him a leading figure in this domain.

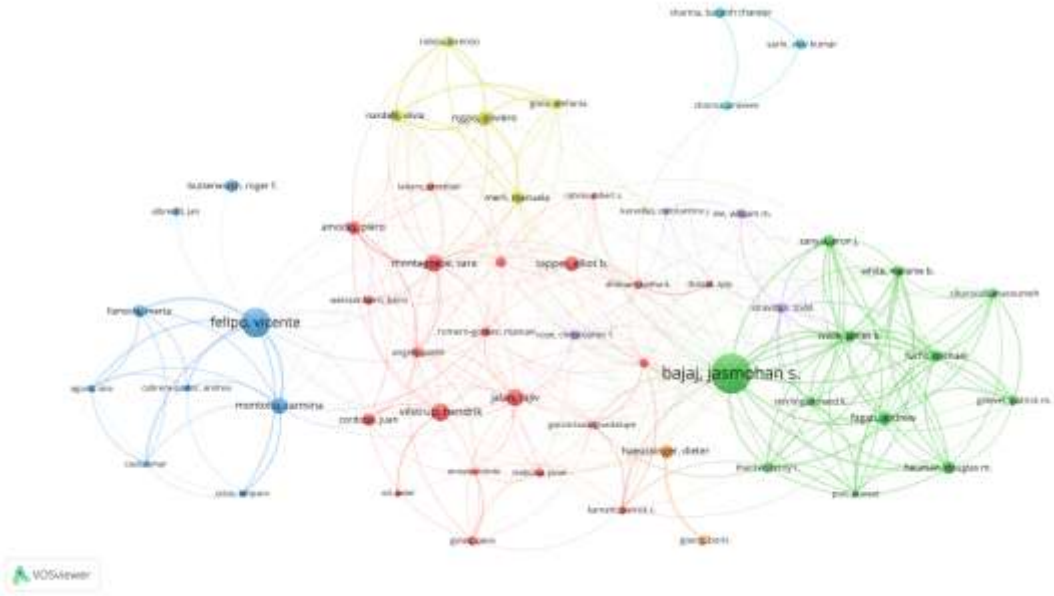

Figure 6. Collaboration network among authors in hepatic encephalopathy research.

Table 2. Top 10 authors with the most publications and citations in the field of hepatic encephalopathy.

author	documents	citations	total link strength
Bajaj, Jasmohan S.	157	10885	614
Felipo, Vicente	114	4555	246
Vilstrup, Hendrik	69	4109	121
Jalan, Rajiv	64	4816	57
Montagnese, Sara	64	2394	151
Montoliu, Carmina	63	2132	153
Tapper, Elliot B.	57	2034	12
Riggio, Oliviero	55	2625	170
Amodio, Piero	51	2927	114
Fagan, Andrew	50	1658	278

3.4 Keyword co-occurrence analysis

To identify research hotspots and thematic clusters, a keyword co-occurrence network was constructed based on the extracted bibliometric data. The analysis involved identifying keywords from article metadata, calculating their co-occurrence frequency, and generating keyword clusters within the network. The ten most frequently occurring keywords included: "hepatic encephalopathy," "cirrhosis," "portal hypertension," "ammonia," "acute liver disease," "liver cirrhosis," "minimal hepatic encephalopathy," "hyperammonemia," "encephalopathy," and "ascites" (Table 3). As shown in Figure 7, the terms "cirrhosis" and "hepatic encephalopathy" functioned as key mediators within the network structure, indicating their centrality to research in this field.

Table 3. Distribution of co-occurrence frequency and association strength of core keywords in the field of hepatic encephalopathy research.

keyword	occurrences	total link strength
hepatic encephalopathy	2291	3082
cirrhosis/liver cirrhosis	1835	2561
portal hypertension	481	814
ammonia	471	863
acute liver failure	427	540
liver transplantation	395	502
minimal hepatic encephalopathy	336	336
hyperammonemia	302	353
encephalopathy	279	307
ascites	251	589

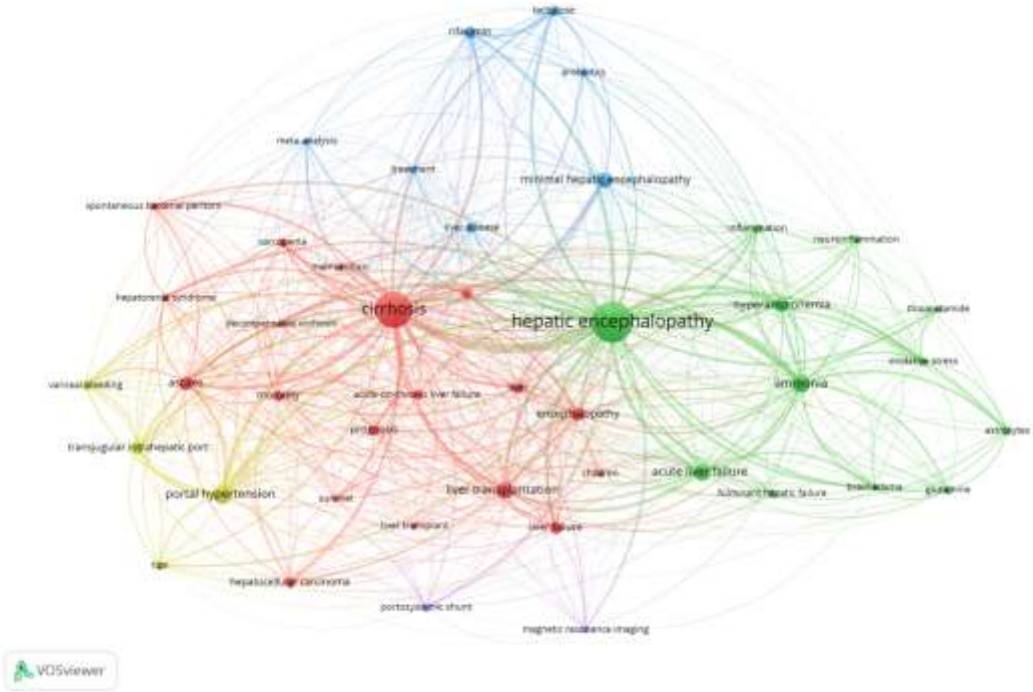

Figure 7. Keyword co-occurrence network in hepatic encephalopathy research.

Keyword burst detection was conducted to reveal emerging trends and visualize recent shifts in research focus. Figure 8 displays the top 25 keywords that experienced significant citation bursts between 2000 and 2024. In the early period (2000–2015), research attention was centered around terms such as "fulminant hepatic failure," "portacaval systemic encephalopathy," "portacaval anastomosis," "amino acids," "magnetic resonance spectroscopy," and "basal ganglia." These keywords reflect foundational research efforts in pathogenesis and neuroimaging.

In more recent years, keywords such as "risk," "American Association," "mortality," "sarcopenia," and "decompensated cirrhosis" have shown marked bursts, indicating a shift in focus toward clinical outcomes, risk stratification, and complications of chronic liver disease. This transition aligns with the growing recognition of hepatic encephalopathy as a major contributor to morbidity and mortality in both acute and chronic liver failure. Consequently, research has increasingly emphasized prognostic evaluation, mechanistic exploration, and the development of novel therapeutic strategies.

These observed keyword bursts not only reflect evolving scientific interests but also provide

valuable insights and directions for future clinical and translational research in hepatic encephalopathy.

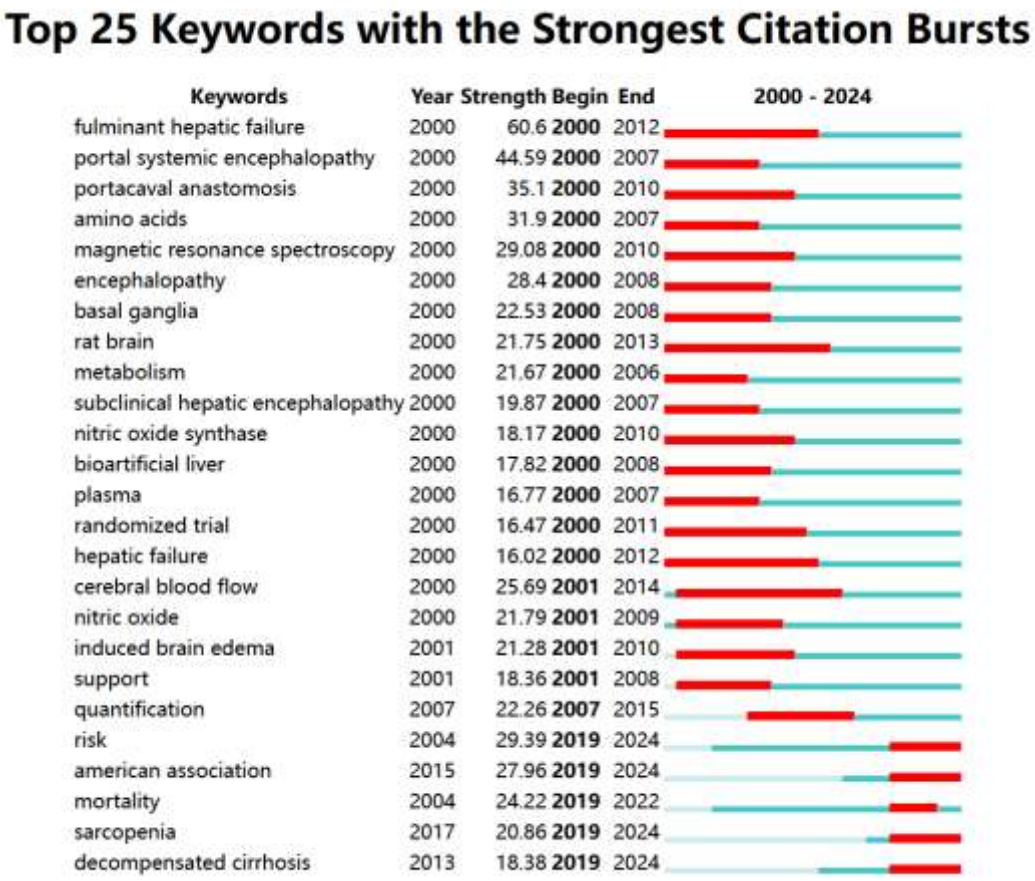

Figure 8. Top 25 keywords with the strongest citation bursts in hepatic encephalopathy research, 2000-2024.

4. Discussion

Metabolic Brain Disease ranks as the most prolific journal in the field and also demonstrates the highest centrality in collaborative networks. Its publication base in the United States may reflect the country's substantial population, economic power, research capacity, technological advancement, and robust healthcare infrastructure. Notably, despite its high publication volume, the journal's Journal Impact Factor (JIF) is relatively modest. This may be attributed to its focus on fundamental aspects of neurological disorders, emphasizing experimental and clinical techniques related to conditions such as stroke, epilepsy, myelin disorders, toxic encephalopathy, alcohol-related brain disease, genetic and metabolic encephalopathies, viral and non-viral encephalitis, and neurodegenerative diseases including Alzheimer's disease. In contrast, *Journal of Hepatology*, with a JIF of 26.8, is the highest-impact journal within the field of Gastroenterology and Hepatology. Although it publishes fewer articles, its academic influence and the quality of its publications are considerable.

This study visualizes and analyzes research output on hepatic encephalopathy (HE) from 2000 to 2024. A total of 8,723 articles were published by 36,291 authors across 7,284 institutions from 119 countries/regions in 1,783 academic journals, citing 15,546 references. The annual publication volume has shown a steady increase, reflecting a growing interest in this field. HE, a neuropsychiatric syndrome secondary to liver dysfunction, represents a major clinical challenge due to its high morbidity, mortality, and financial burden. For instance, in the United States alone, HE accounts for 22,931 hospital admissions annually, with an average hospital stay of 8.5 days and a mean cost of $64,108 per case[12.] Despite

progress in understanding the pathophysiology of HE, clinical advances in diagnostics and treatment have lagged behind. Consequently, there is heightened global interest in elucidating the mechanisms of HE, although comprehensive bibliometric analyses of current research status, trends, and hotspots remain limited.

This study further identifies *risk assessment* as a prominent emerging theme and explores it in detail. Risk assessment facilitates personalized prevention strategies by identifying high-risk individuals. The future of HE management lies in precision medicine—tailoring interventions to individual profiles to prevent overt HE, reduce hospitalization rates, and improve survival outcomes. Continued research on individualized risk stratification is essential to improving the prognosis and quality of life in cirrhotic patients at risk of HE.

4.1 Overview of Major Research Trends and Frontiers

Bibliometric analyses of keyword co-occurrence and citation bursts reveal distinct evolutionary trends and emerging priorities in HE research. The keyword co-occurrence network (Figure 7) maps the core conceptual structure of the field, highlighting three major clusters:

1. **Etiology and pathophysiology**, including keywords such as ammonia, hyperammonemia, acute liver failure, and portosystemic shunting (TIPS).
2. **Clinical phenotypes**, represented by terms like cirrhosis, decompensated cirrhosis, neuropsychological performance, and ascites.
3. **Therapeutic interventions**, such as liver transplantation and management of portal hypertension.

Keyword burst analysis (Figure 8) identifies pivotal research frontiers from 2000 to 2024:

- **Risk stratification and prognostication**, marked by the burst of terms like "risk" (burst strength: 34.56, 2020–2024) and "mortality risk," indicating a paradigm shift toward predictive modeling and individualized patient evaluation.
- **Muscle-wasting syndromes**, with "sarcopenia" (burst strength: 18.72, 2021–2024) emerging as a key biomarker linking malnutrition to disease severity and outcomes.
- **Advanced disease management**, where "decompensated cirrhosis" (burst strength: 16.05, 2022–2024) emphasizes research on end-stage complications.
- **Guideline-informed practice**, signaled by bursts in keywords such as "American Association," reflecting the growing impact of consensus statements (e.g., AASLD, EASL) on clinical protocols.

Emerging research is increasingly interdisciplinary, intersecting along three axes:

1. **Microbiome-gut-liver axis**: Fecal microbiota transplantation (FMT) and probiotics are being investigated to correct dysbiosis and reduce ammonia production.
2. **Nutritional-metabolic integration**: Sarcopenia assessment (e.g., L3 SMI on CT, handgrip strength) and micronutrient repletion (e.g., zinc) are bridging nutrition science with HE pathogenesis.
3. **Technology-enhanced diagnostics**: Artificial intelligence (AI)–based risk prediction models and magnetic resonance spectroscopy are being developed to detect early-stage HE.

The rationale for prioritizing risk assessment is clear: the keyword "risk" not only had the strongest citation burst (2020–2024) but also ranked highest in network centrality. This central positioning connects multiple research dimensions:

- **Etiology**: e.g., ammonia toxicity, sarcopenia
- **Disease staging**: e.g., decompensated cirrhosis
- **Clinical outcomes**: e.g., mortality, rehospitalization
- **Therapeutic interventions**: e.g., nutrition therapy, microbiome modulation

This focus underscores the translational imperative in the field: effective prognostic stratification forms the cornerstone of personalized HE management, guiding prevention, optimizing resource use, and informing therapeutic innovation.

4.1.1 Underlying Liver Disease and Risk Assessment

Hepatic encephalopathy (HE) is not a singular clinical entity; rather, it involves complex interactions primarily between the liver and the brain, and arguably extends to the digestive and nervous systems. The pathophysiological mechanisms underlying HE remain multifaceted and incompletely understood. In the absence of effective treatment of the underlying liver disease, HE is associated with poor survival outcomes, elevated rehospitalization rates[13], impaired health-related quality of life—even in mild cases[14]—and increased mortality risk, particularly in severe forms[14,15]. There exists a direct correlation between HE severity and patient survival, with higher grades corresponding to decreased survival and increased mortality[15]. Survival and mortality are influenced by factors including the type of underlying liver disease, HE severity, presence of complications, and therapeutic interventions[16]. For instance, acute liver failure (type A HE) demonstrates mortality rates ranging from 50% to 80%, especially in grades III–IV, where liver transplantation remains the definitive curative therapy[17,18]. Conversely, type B HE, associated with portosystemic shunting, exhibits relatively higher survival rates; aggressive dietary management and ammonia reduction strategies significantly mitigate mortality[19]. Moreover, within identical underlying liver disease categories, patients classified as grade III–IV exhibit markedly higher mortality compared to grades I–II[20], compounded by increased mortality due to co-infections and hepatorenal syndromes. Hence, early identification of precipitating factors, optimization of comprehensive management, comorbidity control, and timely assessment for liver transplantation are pivotal to improving prognosis.

4.1.2 Nutrition and Risk Assessment

Malnutrition is a common finding among patients with hepatic encephalopathy (HE), characterized by depletion of both adipose tissue and skeletal muscle. Notably, sex-specific patterns are observed, with adipose depletion predominating in females and muscle loss (sarcopenia) more prevalent in males[21]. Sarcopenia, defined as the loss of muscle mass and function, represents a critical facet of malnutrition in cirrhosis. Both malnutrition and sarcopenia are established markers of severe nutritional compromise, as detailed in clinical practice guidelines (CPGs), and have independently been associated with reduced survival and increased incidence of complications such as HE and cirrhosis progression[22]. Accordingly, malnutrition and sarcopenia should be regarded as complications of cirrhosis, with evidence linking them to increased mortality among hospitalized cirrhotic patients and those awaiting liver transplantation, thereby adversely affecting overall prognosis[23,24]. Importantly, sarcopenia has emerged as a significant research focus, as highlighted by its identification as a high burst strength keyword in bibliometric analyses, reflecting its frequent co-occurrence with HE and its profound prognostic implications.

Consequently, systematic and precise assessment of nutritional status—particularly sarcopenia—is essential for guiding effective therapeutic interventions and improving HE outcomes. Such assessments provide critical input for risk stratification concerning HE development, progression severity, mortality, and rehospitalization. However, current guidelines lack clarity on optimal dietary strategies for HE patients complicated by malnutrition and muscle wasting, as well as on standardized approaches for evaluating these nutritional challenges to enhance HE prognosis and survival.

4.1.3 Nutritional Status Assessment for Risk Prediction

This section emphasizes validated nutritional assessment tools specifically applicable to chronic liver disease and cirrhosis. Commonly utilized instruments include the Royal Free Hospital Nutritional Prioritising Tool (RFH-NPT), the Malnutrition Universal Screening Tool (MUST), Nutritional Risk Screening 2002 (NRS-2002), alongside disease severity indices such as the Child-Pugh Score and Model for End-Stage Liver Disease (MELD) Score[25]. The RFH-NPT, designed explicitly for this patient population[26], exhibits prognostic relevance, with score improvements correlating directly with enhanced survival outcomes. The MUST integrates parameters including body mass index (BMI), weight change, and disease status. Additionally, the Hepatic Disease Malnutrition Score (HDMS) is frequently employed in cirrhosis management to evaluate the effects of muscle mass, fat stores, and fluid retention (e.g., oedema, ascites) on nutritional status.

Sarcopenia, recognized both as a complication of liver disease[27] and a pivotal indicator of hepatic malnutrition, is assessed by evaluating muscle mass, fat reserves, and fluid accumulation[28]. The gold standard for sarcopenia measurement is the computed tomography (CT)-derived L3 skeletal muscle index (SMI), with established cut-offs of <50 cm^2/m^2 for men and <39 cm^2/m^2 for women; reduced SMI robustly predicts mortality and HE risk. The psoas muscle, relatively unaffected by physical activity and fluid overload, serves as a critical skeletal muscle marker sensitive to metabolic and molecular disruptions in cirrhosis[29]. While skeletal muscle contractile function has been utilized as an indicator of dystrophy, it does not directly quantify muscle mass. Handgrip strength testing offers a simple, cost-effective, and validated approach for malnutrition detection in cirrhotic patients[30], with diminished grip strength independently forecasting mortality, hospitalization, and HE occurrence. Nonetheless, such functional assessments predominantly depend on subjective patient effort and possess limited negative predictive value.

The Subjective Global Assessment (SGA) utilizes clinical data obtained during patient evaluation to determine nutritional status without reliance on objective measurements[31]. Overall, SGA demonstrates good inter-observer reproducibility and has been correlated with various clinical and prognostic outcomes in the context of liver transplantation[32]. However, SGA exhibits limited concordance with other nutritional assessment methods, such as total lymphocyte count, mid-arm muscle circumference (MAMC), mid-arm muscle area (MAMA), triceps skinfold thickness (TSF), subscapular skinfold thickness, body mass index (BMI), and handgrip strength. Moreover, SGA tends to underestimate muscle loss in patients with liver disease when compared to more objective measures. It is critical to recognize that patients with hepatic encephalopathy (HE) require comprehensive risk assessments encompassing protein tolerance, electrolyte and vitamin deficiencies, precipitating factors, and complications, in addition to basic nutritional and liver function evaluations. Therefore, SGA's utility for precise sarcopenia-driven risk stratification remains limited compared to imaging modalities such as computed tomography (CT) or functional assessments like dynamometry.

Following baseline nutritional assessment, clinical management should incorporate evidence-based recommendations and expert consensus concerning daily caloric intake, protein tolerance, micronutrient deficiencies (notably zinc, detailed below), potential HE precipitants (e.g., infections, gastrointestinal bleeding), concurrent complications (e.g., ascites, renal impairment), and underlying hepatic and metabolic status.

1. **Energy Intake:** Most nutritional intervention studies in cirrhosis advocate provision of at least 35 kcal/kg body weight per day[33], although reductions may be appropriate during acute illness phases. Given the prolonged overnight fasting typical in cirrhotic patients, strategies such as provision of evening snacks (~50 g complex carbohydrates) aim to shorten fasting duration, reduce catabolism, and mitigate associated risks[34]. Frequent meals have been demonstrated to prevent accelerated starvation and proteolysis, leading to improvements in metabolic profiles and quality of life.

2. **Protein Intake (Critical Risk Modifier):** Protein consumption is essential yet controversial in HE management. Approximately 75% of HE patients suffer from moderate to severe protein-calorie malnutrition, characterized by loss of muscle mass and energy stores[35]. These patients exhibit increased protein requirements and are vulnerable to accelerated fasting metabolism, sarcopenia progression, and HE exacerbation, indicating that insufficient protein intake is detrimental[36]. Clinically, low-protein diets should be avoided; instead, small, frequent meals with moderate to high nutritional refeeding are recommended. Oral supplementation is preferred, with enteral (nasogastric tube) or parenteral nutrition employed as necessary. Regulation of ammonia metabolism is fundamental in HE management across all grades[37], and nutritional strategies play a pivotal role. Although transient protein restriction may be necessary during overt HE episodes, rapid reintroduction to target intake (1.2–1.5 g/kg/day) should follow as mental status improves[38]. Emphasis is placed on high-quality proteins, especially vegetable and whey proteins, which yield lower ammonia

production, alongside branched-chain amino acid (BCAA) supplementation.

3. **Micronutrients – Zinc Deficiency (A Modifiable Risk Factor):** The liver is central to metabolic regulation and trace element homeostasis[40], encompassing essential elements such as calcium, iron, magnesium, zinc, copper, manganese, cobalt, selenium, and molybdenum[41]. Acute liver injury induces oxidative stress, marked by elevated free radicals, malondialdehyde (MDA), and oxidized glutathione (GSSG), alongside decreased reduced glutathione (GSH). Concurrently, hepatic concentrations of zinc, copper, manganese, and selenium decline significantly, while iron levels increase[42]. This imbalance exacerbates hepatocyte oxidative damage and apoptosis, additionally promoting pro-inflammatory mediators that elevate mortality risk in HE[43].

Severe zinc deficiency correlates with HE due to impaired ammonia metabolism, secondary to decreased urea cycle enzyme activity[44]. In cirrhosis, an inverse relationship exists between serum zinc and blood ammonia levels[45]. Zinc supplementation enhances ammonia clearance via its role as a cofactor in urea cycle enzymes and can increase serum albumin, which is often reduced in progressive liver disease and may contribute to diminished zinc absorption[46]. Malnutrition in HE patients is partially attributable to micronutrient deficiencies, including zinc[39]. Consequently, zinc deficiency associates with greater cirrhosis severity and higher HE grades, warranting evaluation in all cirrhotic patients with HE and hypoalbuminemia[47]. Beyond metabolic roles, zinc functions as a signaling ion with antioxidant, anti-inflammatory, and anti-apoptotic effects, mitigating oxidative damage by modulating redox reactions of metals such as iron and copper[48,49]. Zinc supplementation (initially 50 mg/day, followed by 25 mg/day maintenance) is recommended, particularly in hypoalbuminemic individuals[22], facilitating urea cycle function and preventing hyperammonemia that precipitates HE.

4.1.3 Gut Flora and Risk Assessment

The gut microbiome has emerged as a pivotal frontier in HE research, evidenced by its strong citation burst in bibliometric analysis (e.g., microbiome, dysbiosis, FMT). Beyond therapeutic targeting, microbial profiling now offers unprecedented potential for predicting HE risk and stratifying patients.

Recent studies have shown that HE treatment targeting the microbiome is promising, and it can be divided into beneficial taxa and harmful taxa reduction, and the regulation of intestinal beneficial flora mainly includes probiotics, prebiotics, synbiotics, antibiotics, intestinal microbial transplantation and traditional Chinese medicine enema, etc. Lactose and Rifaximin, in particular, have been widely used in the clinic[50]. As a non-absorbable disaccharide, lactose can improve the intestinal environment by increasing intestinal peristalsis to promote defecation at the same time, promote the growth environment of beneficial bacteria, and then reduce the production of ammonia. As a first-line treatment drug, it is especially suitable for the prevention and acute attack management of hepatic encephalopathy[51,52].

Fecal metagenomic sequencing reveals distinct microbial patterns associated with HE susceptibility and progression: Depletion of autochthonous taxa (Lachnospiraceae, Ruminococcaceae) coupled with expansion of pathobionts (Enterobacteriaceae, Staphylococcaceae) correlates with hyperammonemia and cognitive impairment[50,55]. Multiple clinical data have shown that probiotics (such as lactobacillus and bifidobacterium) can improve cognitive function in microhepatic encephalopathy by reducing the production of blood ammonia and neurotoxins[53]. At the same time, the synergistic effect of probiotics and probiotics can also improve the diversity of intestinal flora and significantly reduce the incidence of patients with hepatic encephalopathy[54]. Bajaj et al. identified a "HE-risk microbiome" signature (ratio of pathogenic to beneficial taxa > 0.6) predicting 90-day HE-related hospitalization (AUC=0.81)[56].

The current promising therapeutic approach is fecal microbial transplantation, which transfers intestinal flora from healthy donors to patients and re-establishes intestinal flora balance. FMT affects HE through various potential mechanisms, such as changing microbiome community structure, producing SCFAs, reducing ammonia production, and regulating bile acid metabolism[55,56]. Reduced microbial genes for short-chain fatty acid (SCFA)

production (butyrate kinase) and increased urease activity (ureG) predict HE development independent of liver disease severity[55]. Impaired bile acid (BA) transformation by Bacteroidetes (↓ baiCD genes) correlates with neuroinflammation risk[55]. FMT enema has been shown to reduce hospitalization rates and improve cognition and dysbiosis in patients with recurrent HE and cirrhosis[57]. However, at present, standardized protocols for FMT preparation are lacking, the method of preparing FMT, nor have we found the ideal FMT donor, nor have we established the best FMT administration regimen or whether patients need to repeat administration.

4.1.3 Gut Flora and Risk Assessment

The gut microbiome has emerged as a critical frontier in hepatic encephalopathy (HE) research, as reflected by its pronounced citation burst in bibliometric analyses (e.g., terms such as microbiome, dysbiosis, fecal microbiota transplantation [FMT]). Beyond its therapeutic targeting, microbial profiling offers unprecedented potential for predicting HE risk and stratifying patient populations.

Recent studies demonstrate that microbiome-targeted therapies hold promise for HE management, primarily through promoting beneficial taxa and reducing harmful taxa. Approaches to modulate intestinal flora include probiotics, prebiotics, synbiotics, antibiotics, fecal microbial transplantation, and traditional Chinese medicine enemas. Lactulose and rifaximin are widely employed clinically[50]. Lactulose, a non-absorbable disaccharide, improves the intestinal milieu by enhancing peristalsis and promoting defecation, thereby fostering the growth of beneficial bacteria and reducing ammonia production. As a first-line agent, lactulose is especially effective for prevention and acute management of HE episodes[51,52].

Fecal metagenomic sequencing reveals distinct microbial signatures associated with HE susceptibility and progression. Depletion of autochthonous taxa such as Lachnospiraceae and Ruminococcaceae, concomitant with expansion of pathobionts including Enterobacteriaceae and Staphylococcaceae, correlates with hyperammonemia and cognitive impairmen[50,55]. Clinical data further indicate that probiotics—particularly Lactobacillus and Bifidobacterium strains—can improve cognitive function in minimal HE by decreasing blood ammonia and neurotoxin levels[53]. Moreover, synergistic probiotic and prebiotic therapies enhance gut microbial diversity and significantly reduce HE incidence[54]. Bajaj et al. identified an "HE-risk microbiome" signature—defined as a pathogenic-to-beneficial taxa ratio exceeding 0.6—that predicts 90-day HE-related hospitalizations with an area under the curve (AUC) of 0.81[56].This finding highlights the potential of microbial markers in predicting the risk of HE, and emerging clinical models are further improving prediction efficacy by integrating microbial and clinical variables (see Table 4).

Table 4. Emerging clinical models synergize microbial and clinical variables:

Model Component	Clinical Parameters	Microbial Parameters	Risk Prediction Gain
HE occurrence	MELD-Na, Prior HE, Sarcopenia	Enterobacteriaceae abundance, SCFA genes	↑ AUC 0.72 → 0.88[56]
HE recurrence	Psychometric Hepatic Encephalopathy Score (PHES)	Dysbiosis Index*, BA-metabolizing taxa	Sensitivity ↑ 34%[57]
Mortality	ACLF grade, Lactulose use	Urease-producing bacteria, Fecal calprotectin	Hazard ratio ↑ 2.1[58]

*Dysbiosis Index = (Pathobionts) / (Autochthonous taxa)

Among emerging treatments, fecal microbial transplantation (FMT) stands out by restoring intestinal microbial equilibrium through transfer of flora from healthy donors. FMT influences HE pathophysiology via multiple mechanisms, including modulation of microbial community structure, production of short-chain fatty acids (SCFAs), reduction of ammonia synthesis, and

regulation of bile acid metabolism[55,56]. Notably, decreased abundance of SCFA-producing genes (e.g., butyrate kinase) and increased urease gene expression (ureG) predict HE development independently of liver disease severity[55]. Impaired bile acid transformation by Bacteroidetes, marked by reduced baiCD genes, associates with increased neuroinflammation risk[55]. Clinical studies indicate that FMT enemas reduce hospitalization rates and improve cognition and dysbiosis in recurrent HE patients with cirrhosis[57]. However, standardized protocols for FMT preparation, donor selection, administration routes, and dosing regimens remain undeveloped.

Ongoing clinical efforts include: (1) The MICROB-PREDICT consortium, validating a machine-learning model integrating metagenomic data, serum metabolites (e.g., indoxyl sulfate), and MELD score to predict six-month HE risk[55]; (2) The Phase 2 GS-001 trial (NCT04118921), evaluating FMT enema efficacy in HE recurrence prevention, with preliminary data showing a 62% reduction in hospitalizations[56]; and (3) Development of rapid bedside assays for fecal urease activity and Enterococcus quantification for HE risk screening[59].

Epidemiological studies and meta-analyses have also linked Helicobacter pylori infection to increased HE risk[58,59], although further research is warranted to clarify the influence of infection chronicity on HE pathogenesis.

Microbial dysbiosis thus represents not only a therapeutic target but also a quantifiable risk factor. Integration of metagenomic biomarkers (e.g., SCFA biosynthesis genes, dysbiosis indices) with conventional clinical predictors such as MELD and sarcopenia enables precision risk stratification and guides preemptive interventions including probiotic protocols or early FMT. Future therapies may focus on modulating microbiota-host interactions, enhancing gut barrier function, and regulating host immune responses. Given the dynamic influences of pharmacological, dietary, and host factors on the gut microbiota, rigorous trial designs and personalized microbiome-based approaches are essential to optimize treatment efficacy and improve outcomes in HE patients.

5. Limitations

This study has several inherent limitations typical of bibliometric analyses. First, the dataset was restricted to the Web of Science Core Collection (WoSCC) database, excluding other major databases, which may have led to omission of relevant studies. Nevertheless, as established in prior bibliometric research, WoSCC remains the most widely utilized and comprehensive source, adequately reflecting the current landscape of hepatic encephalopathy research. Moreover, differing data ownership structures, file formats, and citation metrics across databases complicate integration, and merging multiple sources may not necessarily enhance analysis quality. Second, we included only English-language publications, potentially underestimating the scholarly contributions from non-English-speaking countries. Third, because the WoSCC database is continually updated, the influence of recently published high-quality articles may be undervalued due to insufficient time for citation accumulation.

6. Conclusion

To our knowledge, this represents the first comprehensive bibliometric analysis of hepatic encephalopathy literature spanning 2000 to 2024. Our findings indicate a growing scholarly interest in hepatic encephalopathy, as reflected by increasing annual publication counts and citation frequencies. The United States and China have emerged as dominant contributors, a status closely linked to substantial funding support. *Metabolic Brain Disease* stands out as the most prolific and influential journal in this domain, with Jasmohan S. Bajaj identified as the leading author.

Keyword co-occurrence analyses highlight ‘risk,’ ‘American Association,’ ‘mortality,’ ‘sarcopenia,’ and ‘decompensated cirrhosis’ as pivotal future research foci warranting further exploration. Bibliometric insights equip researchers—especially newcomers—with a clear understanding of the foundational knowledge framework, including key countries, institutions, authors, and journals, while also illuminating current hotspots and emerging trends. Additionally, this study offers valuable guidance for policymakers and investors, facilitating informed decisions regarding research funding and strategic investment. Notably, risk assessment emerges as a central theme interlinking etiology, clinical manifestations, and therapeutic strategies,

underscoring its critical role in advancing personalized management of hepatic encephalopathy.

Author contributions

DY: Data curation, Software, Supervision, Writing – original draft.

QL: Supervision, Writing – review and editing, Funding acquisition.

XM: Software, Writing – original draft.

CD: Supervision, Writing – review and editing.

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Ethics Statement: This study strictly adheres to the Declaration of Helsinki and relevant ethical guidelines. All the literatures included in the analysis are publicly available academic publications, and the research process did not involve human subjects, animal experiments, or the collection of any original data that requires ethical approval. Therefore, this study does not require additional approval from the ethics committee.

The research data were derived from the Web of Science Core Collection database. The process of data extraction and analysis adhered to the principles of objectivity and impartiality, ensuring academic integrity without data fraud or improper use. All authors declare that there are no conflicts of interest related to this study, and the presentation of research results is not affected by any commercial or academic bias.

Participation and Publication Consent Statement

All individuals involved in the research project, including study participants and contributing authors, hereby provide their informed consent for both participation in the research and the subsequent publication of the work.

Study participants confirm that they have been fully informed about the nature, purpose, procedures, potential risks, and benefits of the research. They understand that their participation is voluntary, that they may withdraw at any time without penalty, and that their personal information will be handled in accordance with applicable privacy laws and ethical guidelines, including anonymization or de-identification where necessary to protect confidentiality. They explicitly consent to the use of their de-identified data, findings, and, where applicable, quotations or case details (with appropriate safeguards) in research outputs and publications.

Contributing authors affirm that they have made substantial contributions to the conception, design, execution, or analysis of the research, and have actively participated in the drafting or revision of the manuscript. They confirm that all data presented are accurate and that any necessary permissions for the use of third-party materials, including copyrighted content, have been obtained. Authors further agree to the order of authorship as listed, acknowledge that there are no undisclosed conflicts of interest, and confirm that all co-authors have reviewed and approved the final version of the manuscript.

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