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Review article

Hepatic encephalopathy post-TIPS: Current status and prospects in predictive assessment

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ABSTRACT

Transjugular intrahepatic portosystemic shunt (TIPS) is an essential procedure for the treatment of portal hypertension but can result in hepatic encephalopathy (HE), a serious complication that worsens patient outcomes. Investigating predictors of HE after TIPS is essential to improve prognosis. This review analyzes risk factors and compares predictive models, weighing traditional scores such as Child-Pugh, Model for End-Stage Liver Disease (MELD), and albumin-bilirubin (ALBI) against emerging artificial intelligence (AI) techniques. While traditional scores provide initial insights into HE risk, they have limitations in dealing with clinical complexity. Advances in machine learning (ML), particularly when integrated with imaging and clinical data, offer refined assessments. These innovations suggest the potential for AI to significantly improve the prediction of post-TIPS HE. The study provides clinicians with a comprehensive overview of current prediction methods, while advocating for the integration of AI to increase the accuracy of post-TIPS HE assessments. By harnessing the power of AI, clinicians can better manage the risks associated with TIPS and tailor interventions to individual patient needs. Future research should therefore prioritize the development of advanced AI frameworks that can assimilate diverse data streams to support clinical decision-making. The goal is not only to more accurately predict HE, but also to improve overall patient care and quality of life.

1. Introduction

The transjugular intrahepatic portosystemic shunt (TIPS) is a cornerstone treatment for portal hypertension secondary to cirrhosis [1,2] and significantly alleviates the symptoms associated with this condition. However, the procedure is not without adverse outcomes, with HE being a notable complication [3].

HE is a neuropsychiatric condition resulting from hepatic insufficiency or portal-systemic shunting that manifests as cognitive dysfunction and may progress to coma [4]. Studies have shown that the

Abbreviations: AI, artificial intelligence; ALBI, albumin-bilirubin; ANN, artificial neural network; AUC, area under the curve; CHE, cholinesterase; CONUT, Controlled Nutritional Status; CT, computed tomography; EHR, electronic health record; FIPS, Freiburg index of post-TIPS survival score; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; IL-6, interleukin-6; ILPD, Indian liver patient dataset; INR, international normalized ratio; LIME, Local Interpretable Model Agnostic Explanation; LR, logistic regression; MELD, Model for End-Stage Liver Disease; ML, machine learning; OHE, overt hepatic encephalopathy; PD, the efficacy of psoas density; PSG, portosystemic gradient; SFAI, subcutaneous fat area index; SHAP, SHapley Additive exPlanations; SVM, support vector machine; TIPS, transjugular intrahepatic portosystemic shunt; VFAI, visceral fat area index.

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incidence of HE after TIPS is as high as 20–50 % [3,5,6], with most cases occurring within one to three months after the procedure [7]. Currently, there is no consensus on the diagnosis of HE [8], and the complex nature of HE significantly prolongs hospital stay, increases healthcare costs, severely diminishes patients' quality of life, and may even increase the risk of mortality [9–12]. Therefore, the predictive identification of high-risk patients for HE after TIPS has become a key focus within the medical community.

In the current clinical landscape, a number of bioindicators and scoring systems are routinely used to assess the potential development of HE following TIPS procedures. Known for their simplicity and user-friendly design, these methods have achieved commendable levels of predictive accuracy within specific clinical scenarios. Their reliance on a spectrum of hepatic biochemical markers, such as albumin, creatinine and total bilirubin, forms the basis of their predictive capacity [13]. In addition, the applicability of these tools is somewhat limited, as they primarily address specific patient populations. For example, the albumin-bilirubin (ALBI) grade, while advantageous in assessing early-stage liver failure, may not be as applicable to the assessment needs of advanced cirrhosis [14]. In addition, these approaches are often inadequate to cover the full continuum of a patient's clinical progression [15]. The infusion of subjective judgments within certain scoring systems introduces an element of variability that, despite its relevance to the diversity of patient presentations, may compromise the accuracy of the scoring results [5,16].

Therefore, there is an imperative within the medical community to establish a scientifically rigorous, objective, and comprehensive assessment framework. Such a framework would improve the diagnostic accuracy of HE and facilitate individualized patient management, thus addressing a significant challenge in the field of hepatic medicine [17].

In this era of rapid scientific and technological progress, artificial intelligence (AI) is gradually expanding its scope of application in the field of medicine [18–22]. In recent years, AI has shown great promise in the evaluation and prognosis of HE. Through the integration of sophisticated machine learning (ML) and deep learning algorithms, AI is capable of mining patient data from various dimensions, thereby improving the accuracy and objectivity of assessment tools used in the management of HE [23].

The purpose of this review is to summarize the use of established tools in the clinical assessment of HE, highlight their inherent limitations, and outline the prevailing and future applications of AI in this context. The intent is to refine healthcare professionals' understanding of post-TIPS HE, improve the accuracy of patient assessments, and expedite the delivery of effective treatments that improve patient health outcomes and reduce mortality.

2. Background of the study

2.1. Overview of TIPS and postoperative complications

TIPS is a minimally invasive interventional therapy primarily used to relieve portal hypertension and its associated complications, such as variceal bleeding and refractory ascites [24]. The TIPS procedure creates an artificial conduit between the intrahepatic portal vein and the hepatic vein, significantly reducing portal system pressure and improving symptomatic manifestations [2,25,26]. This technique has gained wide acceptance in the medical community due to its innovative nature and clinical efficacy [2,27–30]. However, postoperative complications, particularly the development or worsening of HE, remain a significant concern with this procedure [17].

Among the many causative factors of HE, the distinctly induced post-TIPS has attracted significant interest in the medical community due to its unique characteristics. First, the shunt channel created by the TIPS procedure allows portal blood to bypass hepatic filtration and enter directly into the systemic circulation, resulting in physiological changes that reduce the detoxification function of the liver and its ability to filter toxins, particularly ammonia, from the bloodstream [31]. This phenomenon has been associated with a significant increase in both the incidence and severity of HE after TIPS, with rates 20 % to 50 % higher than those observed in HE from other causes [6]. Second, TIPS is typically performed in patients with pre-existing liver disease, such as cirrhosis [29,32]. Individuals with pre-existing conditions are at higher risk of developing HE, which requires more stringent treatment and management protocols. In addition, individuals with post-TIPS HE may have variable responses to conventional therapies such as lactulose or anti-ammonia regimens. This adds another layer of complexity to treatment management and makes their prognosis highly unpredictable - potentially leading to prolonged, recurrent episodes that negatively impact patient quality of life and survival [3,20,33]. Therefore, it is critical to conduct thorough research on post-TIPS HE. Understanding its unique characteristics may help to establish more accurate diagnostic criteria and effective treatment strategies, thereby improving patient quality of life and reducing healthcare costs.

2.2. Definition and mechanisms of TIPS-related HE

TIPS-associated HE is a condition characterized by central nervous system dysfunction due to metabolic changes that occur following the establishment of a shunt connecting the portal vein to the systemic circulation during the TIPS, after exclusion of other known brain disorders [34]. Clinically, this condition is evaluated according to the West Haven criteria [35].

The pathological basis of HE is complicated and involves a spectrum of contributing factors such as liver dysfunction, diversion of visceral blood into the systemic circulation, hyperammonemia, inflammatory response, as well as alterations in gut microbiology, etc., as shown in Fig. 1. The interaction of these factors contributes to the complexity of HE [36–41]. Therefore, the development of effective strategies for the prevention and treatment of HE has been a critical area of medical research.

Accurate prediction and assessment of patient outcomes after TIPS, particularly in terms of early mortality and liver function, as well as identification of individuals at increased risk of HE, can lead to timely and targeted interventions. These can significantly improve patient outcomes and mitigate the broader social and economic impact [13,42]. This review aims to summarize the use and limitations of HE assessment tools currently used in clinical practice, with a particular focus on the nuances of HE after TIPS and the special considerations required for its assessment.

The diagram illustrates the major pathogenic factors contributing to HE after TIPS. It highlights the diversion of visceral blood into the systemic circulation, hyperammonemia, impaired liver function, inflammatory responses, and the role of gut microbiota.

2.3. Factors affecting HE after TIPS

After a rigorous review of the relevant literature and an in-depth examination of post-TIPS HE, we have identified several key factors that are strongly associated with the incidence of HE. These factors include patient baseline characteristics, physiologic and biochemical parameters, medical history, and medication use, which together form a comprehensive framework for assessing the risk of HE after TIPS. Each factor has specific importance and clinical relevance, and the combined effects and cumulative interactions among them are critical in predicting a patient's propensity to develop HE [22,31,43–48].

To illustrate the complexity of these risk factors and their interrelationships after TIPS, we have synthesized our findings into an extensive graph, as shown in Fig. 2. The chat not only provides a visual representation that enhances our understanding of the relationship between risk factors and the development of HE, but also provides valuable guidance for future scientific inquiry and clinical methodology.

The development of HE after TIPS has been conclusively linked to a

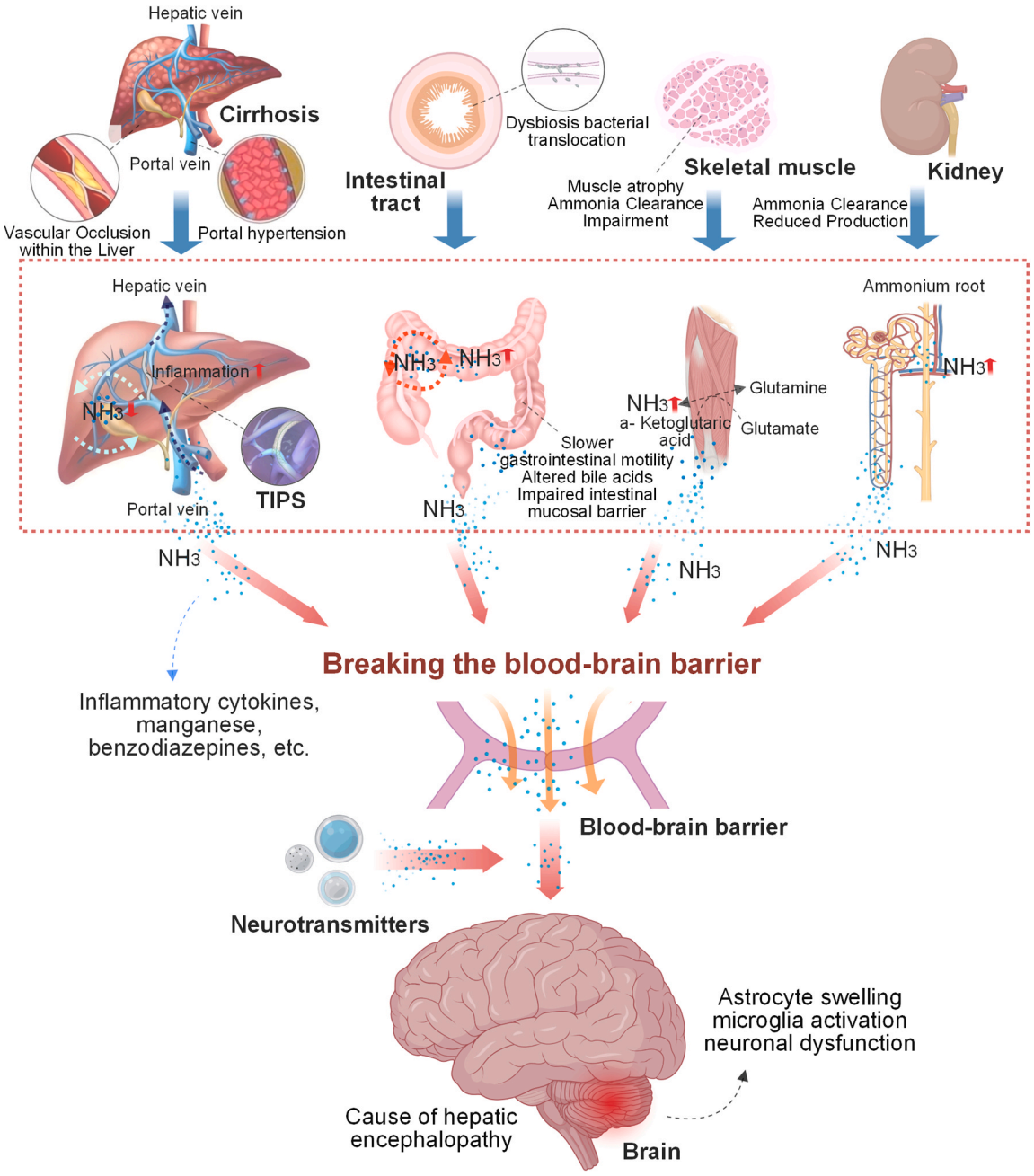

Fig. 1. Mechanisms of HE following TIPS procedure.

variety of factors, with baseline characteristics such as age and liver function serving as prominent predictors [30,32,45,46,50]. Research suggests that patients aged 60 years or older are at significantly higher risk for HE, emphasizing the need for detailed risk assessment within this demographic cohort. Perturbations in serum albumin and bilirubin levels, markers traditionally associated with liver function, may also be indicative of broader health complications, including malnutrition and systemic inflammation [49]. Another key parameter in the assessment of HE risk after TIPS is the portosystemic gradient (PSG), which assesses portal hypertension and hepatic blood flow resistance. Studies have shown that a reduced PSG correlates with an increased risk of HE [50–52], highlighting the need to balance the reduction in PSG with the maintenance of therapeutic efficacy. In addition, the structural aspects of the TIPS procedure, such as stent diameter, type, and anatomical site of puncture, have been shown in recent studies to be critical determinants influencing the development of HE [45].

To improve therapeutic strategies and management after TIPS procedures, it is important to perform continuous health monitoring of patients. This monitoring should extend beyond the monitoring of traditional biochemical markers, such as the international normalized ratio (INR) [45], to include assessment of cognitive function, muscle loss, nutritional status [22], and the effects of certain medications [22,45]. These components can strongly influence the likelihood of developing HE. In particular, factors such as a history of overt hepatic encephalopathy (OHE), diabetes mellitus [46], elevated creatinine levels, decreased serum albumin levels, socioeconomic influences [48,53], and specific etiologies related to cirrhosis [46–48] are all associated with an increased incidence of HE after TIPS. Therefore, it is essential to perform a holistic analysis that takes these factors into account. This will not only anticipate and reduce the risk of HE, but also improve patient outcomes and quality of life.

After assessing the overall health and management needs of TIPS

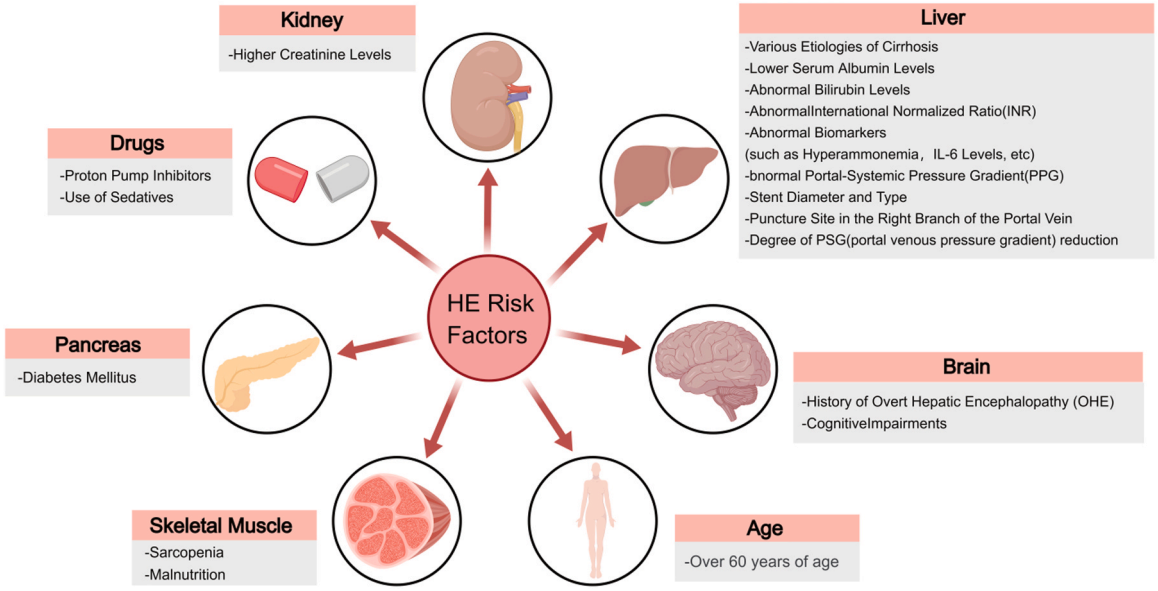

Fig. 2. Risk factors influencing HE after TIPS procedure.

patients, attention shifts to the critical role of biochemical indicators. These indicators are central to predicting the potential onset of HE and informing the approach to its management.

3. Predictive models based on biochemical indicators and their clinical relevance

HE is a common and serious complication that can occur after TIPS procedures. It can lead to an adverse patient prognosis, making effective evaluation and management strategies for HE critical to improving patient outcomes. Clinically, HE is evaluated using a multidimensional approach that includes a thorough history, physical examination, neuropsychological testing, and analysis of various biochemical indicators. These biochemical indicators provide the clinician with direct information about the patient's metabolic state and liver function, which are essential components of the diagnostic framework for HE. Biochemical marker-based scoring systems have been developed to improve the accuracy and reliability of HE assessments. The following sections of this review will discuss 3 major biochemical indicators and 5 major scoring systems in the assessment of HE, with the aim of improving understanding of the range of tools available for the assessment of HE and thus advancing clinical practice.

3.1. Biochemical indicators

Biochemical indicators are critical in the diagnosis and assessment of HE. Critical metrics such as blood ammonia, cholinesterase (CHE), and interleukin-6 (IL-6) levels provide insight into liver function and systemic inflammation relevant to the clinical manifestations of HE.

3.1.1. Ammonia levels

Blood ammonia concentration is a key biomarker in the evaluation of HE and is widely used for the diagnosis and monitoring of this condition [54–58]. Numerous studies show that high blood ammonia levels are closely associated with the occurrence of HE, indicating reduced hepatic detoxification capacity and systemic ammonia accumulation [13,39,59–63]. Research by Yokoyama et al. showed that treatment with rifaximin significantly reduced blood ammonia levels, consistently improved liver function, and improved patients' quality of life [64]. Ochirkhuree et al. highlighted that ammonia levels increase consistently across all stages of HE and established a robust correlation between elevated ammonia concentrations and the Model for End-Stage Liver Disease (MELD) score, confirming the clinical utility of blood ammonia measurements in the assessment of HE [65]. However, several studies have shown that relying solely on blood ammonia levels in the assessment of HE lacks specificity. Overlapping ammonia concentrations have been observed in patients at different disease stages [4]. Patients may develop HE despite normative blood ammonia levels, and various extraneous factors may influence these levels, potentially leading to misdiagnosis [66]. In addition, the rapid variability of ammonia places special demands on sample collection and processing, and these technical challenges may affect its accuracy as a diagnostic tool [67]. As a result, relying solely on blood ammonia metrics to assess HE may be inadequate.

3.1.2. Serum cholinesterase levels

Cholinesterase (CHE) levels have been identified as a critical predictor of the development of HE. Research by Stockhoff et al. found a significant association between reduced CHE levels and increased mortality within one year of HE diagnosis, highlighting its relevance in both acute and chronic liver failure scenarios. This finding underscores the importance of monitoring CHE levels in clinical settings, particularly for post-operative care and prognostication [68,69]. Despite its demonstrated utility, the broader applicability and validation of CHE as a biomarker in different patient demographics requires further investigation. A notable limitation in the current clinical landscape is the lack of CHE measurements in the routine laboratory panels of many medical centers, which may limit its use in clinical practice and lead to underestimation of its prognostic value [66]. Furthermore, relying solely on CHE as a single predictive factor may have limitations. Such an approach may overlook other important factors that contribute to patient outcomes, including overall health status and existing comorbidities. The complexities associated with accurately measuring CHE levels and interpreting their variations across a range of pathological conditions represent an ongoing challenge in the field [70–72].

3.1.3. Monitoring of the inflammatory marker IL-6

Recent medical studies have increasingly recognized the strong association between IL-6 and the risk of developing HE, particularly in patients with underlying cirrhosis [73–75]. Studies by Montoliu, Remmler and others indicate that cirrhotic patients with IL-6 levels above 9 pg/ML have a significantly higher risk of HE [73]. These

findings highlight the importance of monitoring IL-6 as a valuable biomarker for predicting the risk of HE and suggest that its diagnostic utility may exceed that of other indices such as Child-Pugh score and c-reactive protein. However, the predictive ability of IL-6 for HE has certain limitations that need to be considered. IL-6 is a multifunctional cytokine involved in immune regulation, metabolic control, inflammatory responses and neurological modulation. This means that elevated levels of IL-6 do not definitively indicate that a patient will develop HE due to its lack of disease specificity. Furthermore, there is evidence of an association between high IL-6 levels and minimal hepatic encephalopathy in patients with cirrhosis, but the specific pathological mechanisms underlying this association remain unclear. This uncertainty highlights a significant knowledge gap that limits the effectiveness of using IL-6 levels as a definitive screening marker for HE.

Future investigations will focus on improving the accuracy of using IL-6 for clinical prediction and risk stratification. This will include monitoring IL-6 levels over time, investigating the combined effects with additional biomarkers, and assessing the risk of infection in groups with high IL-6 levels [73–75].

3.2. Biochemical parameter-based scoring systems

The Child-Pugh grading system was established in 1964 and has since been a fundamental tool for assessing the risk of liver failure and the potential development of HE. As medical research and technology have advanced, more sophisticated scoring systems have been developed to refine the accuracy of predicting the risk of HE. This review will examine the utility of various scoring systems in the assessment of HE and attempt to elucidate their strengths and limitations in clinical contexts. We expect that this will help to optimize management protocols for patients with HE.

3.2.1. Child-Pugh grading

The Child-Pugh grading system was originally proposed by Child and Turcotte in 1964 and later modified by Pugh et al. in 1972 [76]. It is widely used to measure the severity of cirrhosis [13,77–80]. The Child-Pugh score incorporates variables such as grade of HE, presence of ascites, serum bilirubin level, serum albumin concentration, and prothrombin time, and provides a structured framework for clinical assessment of liver function and overall liver status [76]. Empirical research, including studies by Yang et al., has underscored the effectiveness of the Child-Pugh score in predicting the development of HE, reinforcing its utility in clinical practice [17]. Further innovations in the assessment of HE risk, particularly after TIPS, have been developed by integrating the Child score with radiologic indicators, demonstrating the importance of the Child-Pugh classification [81]. While this classification combines biochemical markers with clinical judgment, it has subjective elements, particularly in the assessment of ascites and HE, which could lead to variability in scoring results[82]. In addition, this system does not include all relevant factors related to liver pathology, with renal function being notably absent. Therefore, the Child-Pugh classification should be used with caution in clinical practice. It should be used in conjunction with other assessment tools when appropriate [76].

3.2.2. Model for End-Stage Liver Disease score

The Model for End-Stage Liver Disease (MELD) score is based on biochemical markers, including bilirubin, the INR and creatinine levels [5,26,81,160]. It also takes into account the etiology of cirrhosis. The MELD score was originally developed to assess the survival prognosis of patients with cirrhosis and to establish prioritization criteria for liver transplant waiting lists [83]. It is based on quantifiable laboratory findings, making it an objective measure and reducing the potential for subjective clinical interpretation. The MELD score has become a benchmark for assessing the urgency of liver transplantation [84]. Clinically, the utility of the MELD score has expanded beyond transplant evaluation to include prognostication of survival outcomes in patients undergoing TIPS procedures and assessment of patients with advanced liver disease prior to transplantation [13,26]. Its significance is also evident in the prediction of HE incidence following TIPS intervention.

Research by Fonio et al. confirmed that MELD grade is an independent risk factor for the development of post-TIPS HE [26,85]. Kim et al. introduced an extension of the MELD model, MELD 3.0, which improves its prognostic accuracy [16]. Despite its utility, the application of the MELD score in clinical practice is not without challenges. In particular, when evaluating patients after TIPS, especially those with impaired renal function or hepatorenal syndrome, the MELD score's heavy reliance on serum creatinine levels may lead to an overestimation of mortality risk. This is particularly relevant in cases where renal function is expected to improve after surgery [86–88]. Given these considerations, it is important to interpret MELD scores with caution and to integrate them into a comprehensive clinical assessment.

3.2.3. Albumin-bilirubin score

The albumin-bilirubin (ALBI) score, developed to assess hepatic synthetic capacity, uses serum albumin and total bilirubin levels as its core parameters [89]. This method was developed to overcome the subjective limitations of clinical assessments such as ascites and HE, which are key components of the Child-Pugh score [14,90–92]. Global implementation has shown that the ALBI score is as valid as, if not superior to, the Child-Pugh score, particularly in patients classified as Child-Pugh class A. Notably, the ALBI score is more accurate in stratifying different prognostic groups. One of the major advantages of the ALBI grade is its simplicity and objectivity, relying solely on quantifiable laboratory values of albumin and bilirubin. This straightforward approach enhances its applicability and facilitates its integration into international clinical research and practice [93]. Despite its advantages, the ALBI score's exclusion of coagulation markers and its failure to directly account for manifestations such as HE and ascites may limit its ability to fully capture a patient's comprehensive clinical situation [14].

3.2.4. Freiburg index of post-TIPS survival

The Freiburg index of post-TIPS survival (FIPS) is a predictive model designed to estimate postoperative survival rates using a combination of biochemical parameters in addition to the patient's age. Key components such as creatinine, bilirubin, albumin and patient age form the basis of this index. Initially, FIPS found its primary application in predicting survival outcomes for patients undergoing TIPS procedures [94,95]. Recent studies have expanded the utility of FIPS by proposing it as a novel and objective marker to assess the risk of HE after TIPS with commendable efficacy [20,22]. Groundbreaking research by Cai's team showed that patients with elevated FIPS scores had a significantly higher incidence of HE compared to their counterparts with lower scores ($P < 0.05$). This suggests that the FIPS score may outperform established models such as the Child-Pugh and MELD scores in predicting HE risk in TIPS patients. However, despite these promising findings, the study's conclusions are tempered by limitations related to sample size. The call for further research through external validation efforts is critical to reliably demonstrate the predictive efficacy of FIPS [94].

3.2.5. Controlled Nutritional Status score

The Controlled Nutritional Status (CONUT) score is an assessment tool that takes into account serum albumin levels, total cholesterol levels, and lymphocyte counts to rapidly determine a patient's nutritional status and guide clinicians in determining appropriate nutritional interventions [83]. In 2022, Li et al. identified a direct relationship between CONUT scores and the risk of OHE. The researchers found that the CONUT score was a better predictor of OHE than other indicators such as neutrophil-lymphocyte ratio, MELD score, and Child-Pugh score. This makes the CONUT score a reliable way to measure the risk of OHE in cirrhotic patients after TIPS [48]. However, the study conducted by Li et al. had limitations due to its retrospective design and the size of its cohort. Therefore, further investigative efforts are needed to confirm the

broader clinical utility of the CONUT score [49].

To assess the risk of HE after TIPS, it is important to consider biochemical markers such as ammonia, CHE, and IL-6, as well as the Child-Pugh, MELD, ALBI, FIPS, and CONUT scoring systems. However, it is important to note that biochemical markers can be influenced by various factors, and scoring systems typically require comprehensive consideration of multiple indicators and clinical presentations to achieve more accurate and comprehensive predictions.

4. Application and Development of AI in HE Prediction

4.1. Accuracy of AI in HE prediction and its optimization methods

The use of AI in predicting HE has shown significant potential. Current AI models, particularly those based on deep learning and ML algorithms, can extract complex patterns from large clinical data sets to achieve highly accurate HE predictions. The accuracy of these models is facilitated by their ability to process multidimensional data, including biomarkers, imaging data, and patient history [96]. Machado et al. performed untargeted metabolomics in 22 cirrhotic patients undergoing elective TIPS placement. They found that pre-existing intrahepatic shunting predicted the severity of HE after TIPS, with specific bile acids inversely correlating with HE grade and metabolomic changes influencing HE progression [97]. However, further improvements in predictive accuracy of HE occurrence will require optimization of data preprocessing and feature engineering to ensure high quality model inputs.

In addition, integrated learning approaches, such as combining results from multiple models, can reduce the bias of individual models and further improve predictive performance. Zhang et al. demonstrated better discrimination in predicting 28-day mortality in patients with HE using ML models such as artificial neural networks (ANNs), which have the potential to improve clinical outcomes for these high-risk patients [18]. In addition, continuous updating and calibration of models to adapt to new data and medical knowledge is an effective strategy to improve the accuracy of HE prediction. Tan et al. demonstrated high diagnostic value in predicting cirrhosis-associated HE using multiple algorithms, including logistic regression (LR), random forests, decision trees, and XGBoost, highlighting the importance of continuous model refinement to keep pace with new information and improve accuracy over time [98].

4.2. The role of AI in clinical decision support: current applications and decision points

AI shows significant potential in the risk assessment of HE after TIPS. AI assists physicians in making accurate decisions regarding diagnosis, treatment selection, and disease monitoring by analyzing clinical and imaging data [99]. In the study by Mehta et al., AI models automatically identified key biomarkers from CT images, predicted the risk of HE, and recommended personalized treatment options.

In addition, AI continuously tracked health indicators and provided timely data support to adjust treatment strategies [100]. The integration of AI not only improved the accuracy of diagnosis and treatment, but also optimized patient management and improved prognosis. Future research is needed to further develop these technologies for broader application in clinical practice, thereby improving medical efficiency and patient care experience [101].

4.3. Aims and prospects of AI-based risk assessment and classification in HE

AI-driven risk assessment and classification of HE aims to achieve precision medicine, ultimately providing highly accurate risk assessment and patient classification tools through personalized analysis [102]. Chen et al. developed a diagnostic model for HE using serum

Table 1
Comparative analysis of scoring systems for predicting HE risk based on biochemical markers post-TIPS.

Test Model	Indicator	Formula/Calculation Method	Application Population	Strengths	Weaknesses	Risk Classification
Child-Pugh Classification [76]	HE grade, ascites, bilirubin, albumin, prothrombin time	Parameters scored 1-3 by severity	Assessment of cirrhotic disease severity	Easy to perform	Subjective parameters may lead to variability in assessment	Grade A: 5-6 points; Grade B: 7-9 points; Grade C: 10-15 points
MELD Score [160]	Bilirubin, INR and creatinine levels, cause of cirrhosis	MELD = 9.57 * loge (creatinine) + 3.78 * loge (bilirubin) + 11.2 * loge (INR) + 6.43 * (cause of cirrhosis)	Prediction of 3-month survival post-TIPS procedure	More precise than Child-Pugh classification for survival prediction	Creatinine component may overestimate risk in some cases	High/Intermediate/Low risk
ALBI Classification [93]	Serum albumin and total bilirubin	ALBI = (log10[total bilirubin] × 0.66) + (serum albumin × −0.085)	patients with cirrhosis and HCC	Simple and objective	May not capture the full complexity of liver dysfunction compared to other scoring systems	ALBI Grade 1/Grade 2/ Grade 3
FIPS[82]	Age, bilirubin, albumin, creatinine	FIPS = 1.43 * log10 (bilirubin) − 1.71 * (1 /creatinine) + 0.02 * age − 0.02 * albumin g/dl + 0.81	Six-month survival post-TIPS implantation for secondary prevention of ascites or variceal bleeding	Exhibits higher predictive capability than Child-Pugh and MELD scores	Prognostic discrimination is inadequate in early TIPS implanted patients; limited by higher cutoff value (FIPS > −0.92)	High risk if FIPS > −0.92
CONUT Score [49]	Serum albumin level, total cholesterol level, lymphocyte count	Based on ranges for each parameter; cumulative score categorizes nutritional status	Assessing individual's health status	Comprehensive assessment focusing on nutritional health indicators	Optimal CONUT score thresholds lack standardization; limited validation studies; does not fully incorporate HE triggers	High-risk (CONUT ≥ 5), low-risk (CONUT < 5)

homocysteine and bile acid levels, which demonstrated significant diagnostic value for HE. Future advances may include real-time dynamic models [103]. These tools will help physicians better understand the specific risk factors of each patient with HE, leading to individualized treatment plans. Future directions include the development of more complex and dynamic models that can learn and update in real time to reflect the latest clinical data and research. In addition, the development of interpretable AI models that provide a transparent basis for decision making will further increase clinicians' trust and confidence in AI tools [104].

4.4. Development process and timeline expectations for AI tools in clinical applications

A systematic timeline is essential for the promotion and dissemination of AI tools into clinical practice. The first phase is model development and validation, which includes verifying the reliability and validity of AI models through large-scale, multicenter clinical trials [105]. The next phase is regulatory approval, which ensures that AI tools meet medical device and software compliance requirements. This is followed by clinical pilot applications to gather feedback and facilitate further optimization through pilot use in selected hospitals or healthcare facilities [106]. Ultimately, widespread adoption and application is expected to occur gradually over the next five to ten years, with AI tools playing a key role in more healthcare scenarios as the technology matures and becomes more widespread [107].

4.5. Potential risks and benefits of AI predictive models and their optimization strategies

AI predictive modeling offers both significant benefits and potential risks in clinical applications. Benefits include improved diagnostic accuracy, personalized treatment plans, and optimal allocation of healthcare resources [108]. However, potential risks include misdiagnosis due to model bias, data breaches, and impaired clinical judgment due to overreliance on AI. To mitigate these risks, rigorous data protection measures must be implemented to ensure patient privacy and data security. Arasteh et al. conducted a study on diagnostic chest X-rays and patient characteristics, demonstrating that differential privacy enhances model training by preserving privacy without significantly affecting accuracy or fairness [109]. In addition, establishing a multilevel model validation and correction mechanism can reduce model bias, thereby improving model reliability and fairness. Regular training and education of healthcare professionals to ensure appropriate judgment and decision-making skills when using AI tools has also been shown to be an effective risk management strategy [110].

5. Advances in the application of AI to the evaluation of HE

Conventional scoring systems and clinical biochemical markers are essential for predicting HE. However, their effectiveness is often hampered by the complex nature of the data and challenges in accurate interpretation [95,111]. In this context, the advent of big data and advances in computational power have paved the way for the application of AI in the medical field. AI techniques, including ML and deep learning algorithms, have revolutionized the approach to HE risk assessment. By processing vast amounts of patient-related data, AI methods can extract critical insights and facilitate the development of scoring models that are more accurate, dynamic, and tailored to individual patient profiles. The integration of imaging and clinical data through AI technologies marks a significant departure from traditional diagnostic and assessment methods.

5.1. Modeling of image-based assessment

Methods using AI based on computed tomography (CT) imaging have been investigated for predicting the risk of HE after TIPS procedure [21,22,112,113]. AI, particularly ML algorithms, have proven useful in analyzing and interpreting large imaging datasets, as shown in Table 2. These state-of-the-art approaches not only autonomously detect and quantify salient imaging features, but also provide enhanced risk assessment by synergizing such features with corroborating clinical evidence. James et al. analyzed abdominal CT scans to determine the amount of subcutaneous and visceral adipose tissue and muscle mass in patients undergoing TIPS. Using both univariate and multivariate logistic regression analyses, they found that relative muscle loss associated with overweight or obesity was a significant risk for mortality after TIPS. Their research also showed that there was no significant correlation between this relative muscle loss and the frequency of HE episodes, highlighting the ability of AI to simplify complex imaging datasets [114]. Cai's team used CT images to assess the efficacy of psoas density (PD) and suggested that PD could predict the onset of HE after TIPS. The predictive accuracy of the inverse stepwise LR model was superior to established scores such as MELD, ALBI, and Child-Pugh score. The integration of AI with CT imaging techniques may help to assess the risk of HE morbidity [115].

The integration of AI with CT imaging underscores a shift toward more nuanced and precise assessments of HE risk after TIPS. By enhancing the ability to analyze complex imaging data and combine it with clinical insights, AI-infused models not only increase the accuracy of predictions, but also contribute to a deeper understanding of the pathomechanisms underlying HE. This synergy between CT imaging and AI technologies holds great promise for advancing patient care, offering new ways to assess HE risk and inform targeted therapeutic interventions, thereby optimizing patient management and outcomes.

5.2. Construction of an integrated assessment model

Integrated predictive models that integrate biochemical markers with imaging information have made notable progress in refining the accuracy of risk assessment for HE after TIPS in AI-assisted evaluation. Zhong et al. used univariate and multivariate LR analyses to identify independent risk factors associated with the occurrence of OHE within 3 months after TIPS, as well as one-year mortality rates and early-onset liver dysfunction. An ANN model and a prognostic line graph were developed that accurately predicted the early onset of OHE, mortality, and liver dysfunction in patients with acute variceal bleeding cirrhosis who underwent early TIPS. AI effectively evaluates the prognosis after TIPS and also provides technical support for identifying patients at high risk for OHE [19]. Wang et al. quantified CT images to measure three body composition metrics and evaluated the association between HE and body composition after TIPS using a multivariate LR model. The results suggest that body composition can be used not only for non-invasive nutritional assessment, but also for predicting the risk of HE in cirrhotic patients after TIPS. The study showed that body composition metrics can be used non-invasively, which goes beyond nutritional assessment and can also serve as predictive indicators for the risk of HE in individuals with cirrhosis after TIPS [42]. Ince et al. used patient clinical profiles coupled with laboratory and imaging data to develop three ML models based on support vector machines (SVM), LR and CatBoost algorithms. The models were effective in identifying individuals at risk of developing HE after TIPS procedure, providing additional resources for patient selection and clinical management [116]. Yang et al. used 12 clinical parameters such as age, etiology of cirrhosis, history of diabetes mellitus, Child-Pugh score/classification, MELD score, and enhanced CT data to create three LR models. These models demonstrated the ability to accurately classify patients based on their risk of developing OHE within 3 months after undergoing TIPS, further confirming that combining AI with clinical and imaging data offers a new way to improve the predictive assessment of HE [17].

The effective use of these predictive models underscores the central role of AI technology in improving risk assessment for HE after TIPS. It

Table 2
Utilization of imaging data as a benchmark in study construction.

Reference	Study design	Number of Patients	Model	Study Content	Main Findings	Limitations
Cai et al. 2022 [115]	Single-institution retrospective study	251 patients	Measurement of PD using SliceOmatic V5.0 software	Prediction of HE post-TIPS using psoas major muscle density.	PD < 51.24 HU increases the risk of HE better than MELD, ALBI and Child-Pugh scores.	Includes only patients with bleeding esophagogastric fundal varices.
Ronald et al. 2020 [114]	Single-institution retrospective study	145 patients	OsiriX software combined with R software to analyze bone, muscle and adipose tissue	The impact of relative oligomyopenia and overobesity on post-TIPS mortality.	Relative oligomyopenia and overobesity were identified as significant predictors of reduced survival after TIPS procedures.	Absence of multiple measures to establish causality.
Wang et al. 2023 [42]	Single-institution retrospective study	191 patients	Quantification of body composition by CT in cirrhotic patients using multivariate LR and nomogram analysis	Evaluation of the predictive value of CT-measured body composition for post-TIPS HE in cirrhotic patients.	Visceral fat area index (VFAI) in male patients and subcutaneous fat area index (SFAI) in female patients were significant predictors of HE after TIPS procedures.	Lack of validation for SFAI and VFAI thresholds in an independent cohort; certain potential confounders were not considered in the analysis.

also catalyzes progress toward more individualized approaches to patient care and therapeutic strategy. See Table 3 for additional information.

6. Limitations of AI predictive modeling and necessary precautions

AI predictive models have demonstrated significant potential and application value in various fields, including healthcare. However, certain non-negligible limitations of these models emerge in practical applications. To ensure the safety and reliability of these models in medical settings, it is critical to understand these limitations and take the necessary precautions.

6.1. Lack of model interpretation and transparency

Many AI predictive models, especially deep learning models, are often considered "black boxes" due to their complex structures and high-dimensional data processing capabilities. These models typically do not provide intuitive explanations or insights into their predictive processes. This lack of transparency is particularly challenging in healthcare applications, where clear and interpretable bases for medical decisions are essential, especially in cases where patients' lives and health are at stake [117]. For example, in the diagnosis of Alzheimer's disease, Das et al. used random forest and SVM models for prediction. Although these models demonstrated 84 % sensitivity and 67 % specificity in diagnosis, their complex decision-making processes made it difficult for physicians to understand the rationale behind their conclusions [118].

The decision-making process of AI models is often difficult to explain, which can lead to questioning of predicted outcomes. In the medical field, healthcare professionals and patients need to understand how a model arrives at a particular conclusion in order to make informed medical decisions [119]. For example, in the diagnosis of HE, models need to provide a clear basis for prediction, rather than just a probability or risk score. To address this challenge, researchers are using tools such as Local Interpretable Model Agnostic Explanation (LIME) and SHapley Additive exPlanations (SHAP) to elucidate the model's decision-making process. In a study, Chen et al. achieved 88.8 % diagnostic sensitivity by analyzing clinical data using Entity-Aware Convolutional Neural Networks [120].

However, even in this scenario, medical professionals still need to use LIME to interpret the predictive basis of the model to ensure the accuracy of the diagnosis. Although tools such as LIME and SHAP play a critical role in elucidating the decision-making process of AI models, these tools have their own limitations. They may not fully capture the complex internal logic of the model or, in some cases, provide interpretations that are too simplistic to meet clinical needs [121].

6.2. Data quality and representativeness issues

Data in the healthcare domain are typically highly sensitive and private, posing significant challenges in obtaining high-quality and

Table 3
A comprehensive summary of research pertaining to AI-enhanced assessment models.

Reference	Study Design	Number of Patients	Model	Study Content	Main Findings	Limitations
Yang et al. 2022[17]	Multicenter retrospective study	276 patients	Incremental complexity model (clinical + biochemical + imaging)	Risk assessment of OHE after TIPS	Sarcopenia increases risk of HE after TIPS	Exclusion of patients with dominant HE, third lumbar vertebra skeletal muscle index measurement inconsistency may affect reliability.
Yang et al. 2021[78]	Retrospective study with randomized groups	185 patients (130 training, 55 validation)	LR analysis based on Combined clinical and imaging model (ModelCI)	Predictive modeling of clinical and imaging features	ModelCI is optimal, area under the curve (AUC) better than single model	Small cohort size; subjective nature of the Child-Pugh score assessment.
İnce et al. 2023 [116]	Retrospective single-center study	327 patients	Support vector machine (SVM), LR, CatBoost	Prediction of HE risk post-TIPS	SVM, LR, and CatBoost exhibited prediction accuracies of 74 %, 75 %, and 73 % respectively; AUC about 0.83	Retrospective study design posing a risk for potential bias; data imbalance addressed with synthetic minority over-sampling technique.
Zhong et al. 2021[19]	Retrospective single-center study	207 patients	ANN model and prognostic nomograms	Prediction of OHE, one-year mortality, and liver function abnormalities	ANN model and nomogram had high predictive accuracy	Selection bias inherent to retrospective studies; no external validation conducted; missing data regarding hepatic venous pressure gradient correlations with post-TIPS prognosis.

sufficiently representative datasets for training AI models. Issues such as incompleteness, heterogeneity, and potential bias in the data can affect the accuracy and reliability of these models [122]. As the data may come from specific patient populations or healthcare organizations, inherent biases may hinder the model's performance across different patient populations or healthcare settings. For example, if a model is trained only on HE patient data from a specific region, it may not accurately predict the conditions of patients from other regions. Gianfrancesco MA, while building a predictive model using electronic health record (EHR) data, found that African American and Latino patients had less data in the EHR, leading to a bias in the disease risk model [123]. In addition, health care data are constantly updated as disease characteristics and treatments evolve, requiring regular model updates to maintain validity [124]. However, the process of regularly collecting, processing, and tagging new data is complex and resource-intensive.

6.3. Model validation and reliability issues

Many AI models lack adequate validation, particularly external validation, during the development phase. These models need to be tested in different environments and patient populations to ensure the broad applicability and reliability of their predictions [125]. For example, Ly et al. collected data from 207,487 patients in 13 clinical datasets and found that traditional training and evaluation methods overestimated model accuracy on external datasets by an average of about 20 % due to hidden dataset and data acquisition bias induced shortcut learning. In contrast, a new approach that estimates data acquisition biases and model shortcuts reduced the model's performance prediction error to within 4 %, highlighting the importance of extensive validation in different settings [126].

In the medical field, model validation requires a rigorous clinical trial and approval process to ensure safety and efficacy. These processes are typically time-consuming and costly, potentially limiting the practical application of such models [127]. In addition, AI models must have strong generalization capabilities to maintain high predictive accuracy across diverse patient populations and varying conditions [128]. Models that are overly dependent on specific patterns or features in the training data may underperform in real-world settings. In 2022, Khan et al. developed the adaptive boosting self-normalized multi-view convolutional neural network for lung cancer nodule detection. This model achieved accuracies of 92 % and 99 % on the Lung Image Database Consortium and Image Database Resource Initiative and Early Lung Cancer Action Program datasets, respectively, demonstrating robust generalization ability [129].

6.4. Special discussion: limitations of complex language generation models

Complex language generation models, such as GPT, show great potential for processing large amounts of textual data. However, their complexity and opacity pose significant challenges in medical applications [130]. Due to difficulties in interpreting their predictions, the output of these models may not be fully trusted in medical decision making, particularly when predicting the risk of complex conditions such as HE. For example, although GPT-3 demonstrated high accuracy in diagnosing common conditions such as upper respiratory tract infections, it failed to correctly identify the condition in one-third of cases involving complex scenarios [131]. In addition, Kanjee et al. found that GPT-3 and GPT-4 performed poorly in terms of diagnostic concordance in complex cases, with GPT-4 achieving the highest diagnostic concordance with the final diagnosis in only 39 % of cases [132].

These models suffer from significant biases and errors when dealing with complex medical scenarios, which limits their trustworthiness in practical clinical applications. The decision basis of complex linguistic generative models is often complex and difficult to understand, and the troubleshooting process is quite difficult, which increases the uncertainty of the model in practical applications [133]. In addition, these models are highly dependent on large amounts of high-quality data; if the data contain noise or bias, the models' predictions may be inaccurate [134]. Regular maintenance is also required to maintain their predictive power, as healthcare data and knowledge are constantly updated.

6.5. Necessary precautions

To address the limitations of AI predictive models, several precautions are necessary to improve their reliability in healthcare applications. First, improving the interpretability of the model is critical. Studies have shown that this can be achieved by introducing interpretation tools, such as LIME or SHAP, and incorporating the expertise of healthcare professionals. These measures can translate the model's prediction process into an easily understandable form, helping healthcare professionals to understand the model's decision-making rationale and performance in complex cases [135].

Second, it is important to ensure the diversity and representativeness of the data, which can enhance the predictive power of the model in different scenarios [136]. Multilevel validation strategies, including internal and external validation, can ensure model stability and generalizability [137]. Li developed a framework for quantifying uncertainty in complex systems, which improved model credibility by combining multiple levels of model calibration and validation methods [21]. Continuous involvement and feedback from experts help to adjust and optimize the model, thereby improving its clinical applicability [138].

Finally, a mechanism for regular model updates has been established to ensure that the model consistently reflects the latest medical data and knowledge, thereby maintaining the validity and reliability of predictions [139]. These measures increase the value of AI modeling in medicine, particularly in the prediction and management of specific diseases such as HE. Ongoing updates and integration of current research strengthen the effectiveness of the model in clinical applications, providing significant benefits to patient care and outcomes.

7. Future directions and perspectives

Scoring systems and methodologies are critical tools for assessing the risk of HE following TIPS procedures. These scoring frameworks incorporate the analysis of biochemical parameters, imaging studies, and the integration of advanced computational strategies. Currently, AI algorithms play a pivotal role in various fields, including biomics and healthcare data analysis [140–148]. The fusion of AI techniques with biochemical and radiological data is increasingly recognized for its potential to improve the accuracy of diagnostic and risk stratification processes in the context of HE.

7.1. Refinement of the scoring systems and the research trajectories

Scoring systems such as MELD, Child-Pugh, ALBI, FIPS, and CONUT are critical in assessing patient status and predicting surgical risk. However, they have limitations; for example, they may not fully reflect the true complexity of a patient's condition. Future research should focus on optimizing these systems to improve their predictive accuracy and clinical applicability. In particular, these scoring metrics need to be validated through multicenter studies to ensure their robustness and efficacy. In addition, the incorporation of clinical decision support frameworks can significantly improve model comprehensibility and utility. These advances are likely to improve the effectiveness of scoring systems in clinical practice and provide healthcare providers and patients with a clearer understanding of these methodologies. As a result, more precise individualized treatment protocols can be facilitated.

7.2. The emerging role and future of AI in predicting HE post-TIPS

The medical field has seen remarkable advances in AI, particularly in disease prediction and assessment [149–152]. Cutting-edge technologies have not only made significant breakthroughs in algorithm development and computational power, but have also demonstrated extraordinary capabilities in managing complex medical data sets. AI applications in medical research include early-stage analyses of non-imaging data, as demonstrated by Hou et al. who used neural network models to predict survival in patients with liver disease [153]. This extends to more comprehensive analyses of imaging data, as demonstrated by the use of deep convolutional neural networks to analyze CT scan data by Wang et al. Their work autonomously determines muscle mass from CT images to predict clinical outcomes for individuals with liver disease [154]. The guide to deep learning in healthcare highlights the growing importance of AI technology in areas such as computer vision, natural language processing, and reinforcement learning [149]. At the same time, large-scale language models such as ChatGPT have shown promising capabilities for interpreting clinical data and assessing health conditions such as cirrhosis and hepatocellular carcinoma (HCC). Gilson et al. analyzed ChatGPT's ability to answer applied knowledge test questions related to primary care, particularly those involving histological image analysis [155]. These investigations unfold the diverse utility of AI technology in healthcare paradigms [155–157]. Given the rapid and generative advancement of AI technology, image interpretation capabilities have now been introduced into large-scale language models such as ChatGPT-4.0 and Google Bard, which can provide new insights into healthcare practices [158]. Mallio et al. investigated the use of these models in radiology [159]. These studies refine current diagnostic and therapeutic methods and offer new perspectives for medical research.

Future research should prioritize the implementation of sophisticated ML and deep learning algorithms in the clinical management of HE. This includes, but is not limited to, developing AI paradigms that can process and interpret large, multidimensional medical data sets, exploring the use of AI in detecting early signs of HE progression, and assisting clinicians in developing personalized treatment plans. In addition, the application of advanced technologies such as reinforcement learning and natural language processing may provide new insights into the pathological mechanisms of HE and improve patient management.

7.3. Relevant data repositories

To improve the accuracy of predicting HE risk after TIPS procedures, and to maximize the use of deep learning and extensive language models, high-quality data and strong analytical frameworks are needed. In this context, open access datasets and models are valuable assets. Not only do they allow researchers to authenticate novel algorithms and methods, but they also foster collaboration and resource sharing within the international scientific community. Publicly available datasets relevant to cirrhosis are listed in Table 4, and open-source predictive models for liver pathologies are listed in Table 5. The use of openly available tools is critical to maintaining scientific integrity and accelerating technological advances.

Table 4
Open source datasets related to cirrhosis.

Dataset Name	Data Features	Data Address
UCI ML Repository: Cirrhosis Patient Survival Prediction Dataset	Comprises data elements including Patient ID, survival duration, clinical status, types of medications administered, demographic variables (age, gender), and clinical signs (ascites, hepatomegaly, spider nevi), edema presence, along with various hematological parameters.	https://archive.ics.uci.edu/ML/datasets/cirrhosis
Liver Disorders Dataset (LDDS)	Encompasses predominantly hematological markers such as mean corpuscular volume, alkaline phosphatase, alanine transaminase, aspartate transaminase, and gamma-glutamyl transferase.	https://archive.ics.uci.edu/ML/datasets/Liver+Disorders
Pipeline for Automated Deep Learning Liver Segmentation (PADLLS) (LiTS-Liver Tumor Segmentation Challenge)	An advanced deep learning architecture for automated hepatic CT scan segmentation, integrating 2D and 3D convolutional networks to enhance delineation precision - notably efficacious in ascites cases.	https://github.com/klin059/lits
Duke Liver Dataset (DLDS)	Contains data for abdominal MRI-based liver segmentation primarily targeting populations presenting with cirrhotic liver morphology.	https://zenodo.org/record/7774566

8. Conclusions

This review provides an in-depth examination of the myriad risk factors, assessment tools, and predictive approaches associated with HE after TIPS intervention. It examines the critical role of established scoring systems, including MELD, Child-Pugh, ALBI, FIPS, and CONUT, while acknowledging their limitations. The review highlights the urgent need for future research to refine these indices to improve their accuracy and applicability in the clinical setting. In addition, the document explores the emerging role of AI in predicting HE post-TIPS, highlighting the importance of deep learning and ML in medical imaging analysis and clinical data management. These cutting-edge technologies promise new insights and methodologies for the prediction and management of HE, potentially revolutionizing clinical diagnostics and therapeutic approaches.

In conclusion, this review addresses the multifaceted nature of HE after TIPS and serves as a roadmap for future investigations. It highlights the need to improve existing scoring systems and integrate AI technologies. Future efforts should aim to improve our understanding in these areas, with the goal of increasing the accuracy of HE prediction after TIPS, refining patient management strategies, and ultimately improving patient quality of life and survival.

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CRediT authorship contribution statement

Chujun Weng: Visualization, Methodology, Investigation. **Rongwen Yu:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Qi Zhao:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Shichao Quan:** Writing – review & editing,

Table 5
Models for liver disease prediction available in open source.

Model Name	Role	Address
Liver Disease Prediction Using Various Classifiers	Implementation of diverse ML classifiers on a dataset comprising liver disease patient records to prognosticate liver disease manifestation.	https://github.com/alekha1234/Liver_Disease_Prediction
Imaging Histology Toolkit for Liver Disease Analysis	An open-source Python toolkit that facilitates the extraction of imaging histology features from medical scans, applicable to the analysis of liver cirrhosis in images.	https://github.com/AIM-Harvard/pyradiomics
ML for Liver Disease Prediction	A ML classifier developed specifically to liver diseases.	https://github.com/chollette/Liver-Disease-Classification-Azure-ML-Capstone-Project
Liver Disease Prediction	Predicts liver disease.	https://github.com/DPsalmist/Liver-Disease-Prediction
Predictive Modeling for Pharmacologic Liver Injury	Utilizes a binary classification framework to forecast clinically significant drug-induced liver injury based solely on molecular structure characteristics of pharmaceutical agents.	https://github.com/cptbern/QSAR_DILI_2019
Multilayer Perceptron and XGBoost for Liver Disease Prediction on the Indian Liver Patient Dataset (ILPD) Dataset	Application of advanced ML techniques, namely multilayer perceptron and XGBoost algorithms, on the ILPD to predict liver disease outcomes.	https://github.com/saiivarma/Liver-Disease-Prediction

Supervision, Project administration, Funding acquisition, Conceptualization. **Ziyang Zhang:** Writing – original draft, Investigation, Data curation. **Boxiang Wang:** Visualization, Methodology, Investigation. **Xiaojie Yang:** Visualization, Methodology, Investigation. **Xiaowei Xu:** Writing – original draft, Investigation, Data curation. **Yun Yang:** Writing – original draft, Investigation, Data curation. **Xinru Tan:** Writing – original draft, Investigation, Data curation.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

[1] Hung ML, Lee EW. Role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension: review and update of the literature. Clin Liver Dis 2019;23:737–54.
[2] Boike JR, Thornburg BG, Asrani SK, et al. North American practice-based recommendations for transjugular intrahepatic portosystemic shunts in portal hypertension. Clin Gastroenterol Hepatol 2022;20:1636–62.
[3] Casadaban LC, Parvinian A, Minocha J, et al. Clearing the confusion over hepatic encephalopathy after tips creation: incidence, prognostic factors, and clinical outcomes. Dig Dis Sci 2015;60:1059–66.
[4] Lu K. Cellular pathogenesis of hepatic encephalopathy: an update. Biomolecules 2023;13(2):396.
[5] Fonio P, Discalzi A, Calandri M, et al. Incidence of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt according to its severity and temporal grading classification. La Radiol Med 2017;122:713–21.
[6] Schindler P, Heinzow H, Trebicka J, et al. Shunt-Induced Hepatic Encephalopathy in TIPS: Current Approaches and Clinical Challenges. J Clin Med 2020;9(11):3784.
[7] Rössle M. TIPS: 25 years later. J Hepatol 2013;59:1081–93.
[8] Thabut D, Bouzbib C, Meunier L, et al. Diagnosis and management of hepatic encephalopathy: The French recommendations. Liver Int 2023;43:750–62.
[9] Stepanova M, Mishra A, Venkatesan C, et al. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States From 2005 to 2009. Clin Gastroenterol Hepatol 2012;10:1034–41.
[10] Montagnese S, Rautou P-E, Romero-Gómez M, et al. EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. J Hepatol 2022;77:807–24.
[11] Lee EW, Kuei A, Saab S, et al. Nationwide trends and predictors of inpatient mortality in 83884 transjugular intrahepatic portosystemic shunt. World J Gastroenterol 2016;22:5780–9.
[12] Saab S, Zhao M, Asokan I, et al. History of hepatic encephalopathy is not a contraindication to transjugular intrahepatic portosystemic shunt placement for refractory ascites. Clin Transl Gastroenterol 2021;12(8):e00378.
[13] Peng Y, Wei Q, Liu Y, et al. Prediction and risk factors for prognosis of cirrhotic patients with hepatic encephalopathy. Gastroenterol Res Pract 2021;2021:5623601.
[14] Demirtas CO, D'Alessio A, Rimassa L, et al. ALBI grade: evidence for an improved model for liver functional estimation in patients with hepatocellular carcinoma. JHEP Rep 2021;3:100347.
[15] Vidal-Cevallos P, Chávez-Tapia NC, Uribe M. Current approaches to hepatic encephalopathy. Ann Hepatol 2022;27:100757.
[16] Kim WR, Mannalithara A, Heimbach JK, et al. MELD 3.0: the model for end-stage liver disease updated for the modern era. Gastroenterology 2021;161:1887–95.
[17] Yang C, Zhu X, Liu J, et al. Development and validation of prognostic models to estimate the risk of overt hepatic encephalopathy after tips creation: a multicenter study. Clin Transl Gastroenterol 2022;13(3):e00461.
[18] Zhang Z, Wang J, Han W, et al. Using machine learning methods to predict 28-day mortality in patients with hepatic encephalopathy. BMC Gastroenterol 2023;23(1):111.
[19] Zhong B-Y, Wang W-S, Shen J, et al. Single-Centre Retrospective Training Cohort Using Artificial Intelligence for Prognostic Prediction of Encephalopathy, Mortality, and Liver Dysfunction after Early TIPS Creation. Cardiovasc Interv Radiol 2021;44:1597–608.
[20] Luo S, Zhou Z-M, Guo D-J, et al. Radiomics-based classification models for HBV-related cirrhotic patients with covert hepatic encephalopathy. Brain Behav 2021;11(2):e01970.
[21] Cao J, Yang J, Ming Z, et al. A radiomics model of liver CT to predict risk of hepatic encephalopathy secondary to hepatitis B related cirrhosis. Eur J Radiol 2020;130:109201.
[22] Cheng S, Yu X, Chen X, et al. CT-based radiomics model for preoperative prediction of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Br J Radiol 2022;95(1132):20210792.
[23] Chen X, Wang T, Ji Z, et al. 3D automatic liver and spleen assessment in predicting overt hepatic encephalopathy before TIPS: a multi-center study. Hepatol Int 2023;17:1545–56.
[24] Wang L-J, Yao X, Qi Q, et al. Prevention and treatment of hepatic encephalopathy during the perioperative period of transjugular intrahepatic portosystemic shunt. World J Gastrointest Surg 2023;15(8):1564–73.
[25] de Wit K, Schaapman JJ, Nevens F, et al. Prevention of hepatic encephalopathy by administration of rifaximin and lactulose in patients with liver cirrhosis undergoing placement of a transjugular intrahepatic portosystemic shunt: a multicentre randomised, double blind, placebo controlled trial. BMJ Open Gastroenterol 2020;7(1):e000531.
[26] Wang Z, Wu Y-F, Yue Z-D, et al. Comparative study of indocyanine green-R15, Child-Pugh score, and model for end-stage liver disease score for prediction of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. World J Gastroenterol 2021;27(5):416–27.
[27] Tripathi D, Bureau C. Prophylactic embolization of large spontaneous portosystemic shunts with transjugular intrahepatic portosystemic shunt: A panacea for post-TIPS hepatic encephalopathy? Hepatology 2022;76(3):551–3.
[28] Zuo K, Wang C, Wang J, et al. Transjugular intrahepatic portosystemic shunt through left branch versus right branch of portal vein: a meta-analysis. Abdom Radiol 2021;46(4):1718–25.
[29] Tripathi D, Stanley AJ, Hayes PC, et al. Transjugular intrahepatic portosystemic stent-shunt in the management of portal hypertension. Gut 2020;69(7):1173–92.
[30] Yang C, Chen Y, Wang C, et al. Portal flow diversion based on portography is superior than puncture site in the prediction of overt hepatic encephalopathy after TIPS creation. BMC Gastroenterol 2022;22(1):363.
[31] Li X, Partovi S, Coronado WM, et al. Hepatic Encephalopathy After TIPS Placement: Predictive Factors, Prevention Strategies, and Management. Cardiovasc Interv Radiol 2022;45(5):570–7.
[32] Angeli P, Bernardi M, Villanueva C, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406–60.

[33] Tapper EB, Zhao L, Nikirk S, et al. Incidence and Bedside Predictors of the First Episode of Overt Hepatic Encephalopathy in Patients With Cirrhosis. J Am Coll Gastroenterol 2020;115(12):2017–25.
[34] Riggio O, Nardelli S, Moscucci F, et al. Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt. Clin Liver Dis 2012;16(1):133–46.
[35] Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study Of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60(2):715–35.
[36] Gairing SJ, Schleicher EM, Galle PR, et al. Prediction and prevention of the first episode of overt hepatic encephalopathy in patients with cirrhosis. Hepatol Commun 2023;7(4):e0096.
[37] Rowley MW, Choi M, Chen S, et al. Refractory Hepatic Encephalopathy After Elective Transjugular Intrahepatic Portosystemic Shunt: Risk Factors and Outcomes with Revision. Cardiovasc Interv Radiol 2018;41:1765–72.
[38] Gairing SJ, Müller L, Kloeckner R, et al. Review article: post-TIPSS hepatic encephalopathy—current knowledge and future perspectives. Aliment Pharmacol Ther 2022;55(10):1265–76.
[39] Zhu R, Liu L, Zhang G, et al. The pathogenesis of gut microbiota in hepatic encephalopathy by the gut-liver-brain axis. Biosci Rep 2023;43(6):BSR20222524.
[40] Elsaid MI, Rustgi VK. Epidemiology of Hepatic Encephalopathy. Clin Liver Dis 2020;24(2):157–74.
[41] Wang X, Luo X, Yang L. Risk Factors for Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt: Beyond Stent Diameter. Dig Dis Sci 2021;66:4568–9.
[42] Wang C, Teng Y, Gao J, et al. Low adipose tissue index as an indicator of hepatic encephalopathy in cirrhotic patients following transjugular intrahepatic portosystemic shunt. Abdom Radiol 2023;48(4):1454–67.
[43] Häussinger D, Dhiman RK, Felipo V, et al. Hepatic encephalopathy. Nat Rev Dis Prim 2022;8(1):43.
[44] Yin X, Zhang F, Guo H, et al. A nomogram to predict the risk of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in Cirrhotic Patients. Sci Rep 2020;10(1):9381.
[45] Coronado WM, Ju C, Bullen J, et al. Predictors of Occurrence and Risk of Hepatic Encephalopathy After TIPS Creation: A 15-Year Experience. Cardiovasc Interv Radiol 2020;43:1156–64.
[46] Gairing SJ, Schleicher EM, Labenz C. Diabetes mellitus-risk factor and potential future target for hepatic encephalopathy in patients with liver cirrhosis? Metab Brain Dis 2023;38(5):1691–700.
[47] Helzberg JH, Dai R, Muir AJ, et al. Socioeconomic Status Is Associated with the Risk of Hepatic Encephalopathy after Transjugular Intrahepatic Portosystemic Shunt Creation. J Vasc Interv Radiol 2021;32(7):950–60.
[48] Neff G, III WZ. Systematic Review of the Economic Burden of Overt Hepatic Encephalopathy and Pharmacoeconomic Impact of Rifaximin. Pharmacoeconomics 2018;36:809–22.
[49] Li J, Feng D, Pang N, et al. Controlling nutritional status score as a new indicator of overt hepatic encephalopathy in cirrhotic patients following transjugular intrahepatic portosystemic shunt. Clin Nutr 2022;41(2):560–6.
[50] Li W, Duan Y, Liu Z, et al. Clinical value of hemodynamic changes in diagnosis of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Scand J Gastroenterol 2022;0:1–6.
[51] Luo S-H, Zhou M-M, Cai M-J, et al. Reduction of portosystemic gradient during transjugular intrahepatic portosystemic shunt achieves good outcome and reduces complications. World J Gastroenterol 2023;29(15):2336.
[52] Xia Y, Tie J, Wang G, et al. Individualized portal pressure gradient threshold based on liver function categories in preventing rebleeding after TIPS. Hepatol Int 2023;17(4):967–78.
[53] Liao Y, Zhang L, Wang J, et al. A novel nomogram predicting overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in portal hypertension patients. Sci Rep 2023;13(1):15244.
[54] Tapper EB, Bajaj JS. Ammonia predicts clinical outcomes in cirrhosis –but there are caveats to consider. J Hepatol 2023;79(6):e238–9.
[55] Tranah TH, Ballester M-P, Carbonell-Asins JA, et al. Plasma ammonia levels predict hospitalisation with liver-related complications and mortality in clinically stable outpatients with cirrhosis. J Hepatol 2022;77(6):1554–63.
[56] Ridola L, Riggio O. Ammonia and prognosis of cirrhosis: A new perspective for identifying high-risk patients. J Hepatol 2023;78(2):e69–70.
[57] Pasqualotto E, Cretaio E, Scaramuzza M, et al. Optical System Based on Nafion Membrane for the Detection of Ammonia in Blood Serum Samples. Biosensors 2022;12(12):1079.
[58] Fiati Kenston SS, Song X, Li Z, et al. Mechanistic insight, diagnosis, and treatment of ammonia-induced hepatic encephalopathy. J Gastroenterol Hepatol 2019;34(1):31–9.
[59] Ballester MP, Tranah TH, Balcar L, et al. Development and validation of the AMMON-OHE model to predict risk of overt hepatic encephalopathy occurrence in outpatients with cirrhosis. J Hepatol 2023;79(4):967–76.
[60] Wang J, Zhang Y, Xiang Z. Changes of Plasma Blood Ammonia Levels of Chinese Healthy People and the Establishment of Reference Intervals. Clin Lab 2023;69(1):9.
[61] Direkze S, Jalan R. Diagnosis and Treatment of Low-Grade Hepatic Encephalopathy. Dig Dis 2015;33(4):562–9.
[62] Sedik AA, Hassan A, Saleh DO. Neuromodulatory role of L-arginine: nitric oxide precursor against thioacetamide-induced-hepatic encephalopathy in rats via downregulation of NF-κB-mediated apoptosis. Environ Sci Pollut Res 2023;30(35):84791–804.
[63] Ge PS, Runyon BA. Serum Ammonia Level for the Evaluation of Hepatic Encephalopathy. JAMA 2014;312(6):643–4.
[64] Yokoyama K, Fukuda H, Yamauchi R, et al. Long-Term Effects of Rifaximin on Patients with Hepatic Encephalopathy: Its Possible Effects on the Improvement in the Blood Ammonia Concentration Levels, Hepatic Spare Ability and Refractory Ascites. Medicina 2022;58(9):1276.
[65] Ochirkhuree B, Namdag B, Jambal S, et al. Elevated Ammonia Level as a Diagnostic Marker of Hepatic Encephalopathy. Cent Asian J Med Sci 2016;2(1):54–60.
[66] Murakami T, Shimizu H, Yogi N, et al. A Case of Perihilar Cholangiocarcinoma with Postoperative Hepatic Encephalopathy Due to Portosystemic Shunt Treated by Percutaneous Embolization. Gan Kagaku Ryoho Cancer Chemother 2023;50(1):102–4.
[67] Xu X-Y, Ding H-G, Li W-G, et al. Chinese guidelines on management of hepatic encephalopathy in cirrhosis. World J Gastroenterol 2019;25(36):5403–22.
[68] Stockhoff L, Muellner-Bucsics T, Markova AA, et al. Low Serum Cholinesterase Identifies Patients With Worse Outcome and Increased Mortality After TIPS. Hepatol Commun 2022;6(3):621–32.
[69] Tan L, Meng Y, Zeng T, et al. Clinical diagnostic significance of prealbumin, cholinesterase and retinol binding protein in liver cirrhosis combined with encephalopathy. Br J Biomed Sci 2019;76(1):24–8.
[70] Aghdassi A, Schwedhelm E, Atzler D, et al. The relationship between homoarginine and liver biomarkers: a combination of epidemiological and clinical studies. Sci Rep 2023;13(1):5230.
[71] Decker SO, Krüger A, Wilk H, et al. Concurrent Change in Serum Cholinesterase Activity and Midregional-Proadrennomedullin Level Could Predict Patient Outcome following Liver Transplantation. Biomolecules 2022;12(7):989.
[72] Liu D, Li J, Lu W, et al. Gamma-glutamyl transpeptidase to cholinesterase and platelet ratio in predicting significant liver fibrosis and cirrhosis of chronic hepatitis B. Clin Microbiol Infect 2019;25(4):514e1–8.
[73] Labenz C, Toenges G, Huber Y, et al. Raised serum Interleukin-6 identifies patients with liver cirrhosis at high risk for overt hepatic encephalopathy. Aliment Pharmacol Ther 2019;50(10):1112–9.
[74] Li J, Liu Y, Li M, et al. Association of preoperative IL-6 levels with overt HE in patients with cirrhosis after TIPS. Hepatol Commun 2023;7(4):e1028.
[75] Gairing SJ, Anders J, Kaps L, et al. Evaluation of IL-6 for Stepwise Diagnosis of Minimal Hepatic Encephalopathy in Patients With Liver Cirrhosis. Hepatol Commun 2022;6(5):1113–22.
[76] Pugh RNH, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60(8):646–9.
[77] Zhou G-P, Jiang Y-Z, Sun L-Y, et al. Early transjugular intrahepatic portosystemic shunt for acute variceal bleeding: a systematic review and meta-analysis. Eur Radiol 2021;31:5390–9.
[78] Yang Y, Fu S, Cao B, et al. Prediction of overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt treatment: a cohort study. Hepatol Int 2021;15:730–40.
[79] Wang Q, Bai W, Han G. Freiburg index of post-TIPS survival: The first score for individual prediction and a complementary tool for risk stratification. J Hepatol 2021;75(3):747–9.
[80] Liu J, Zhou C, Wang Y, et al. The combination of Child-Pugh score and quantitative CT-based spleen volume could predict the risk of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt creation. Abdom Radiol 2021;46:3464–70.
[81] Yang Y, Liang X, Yang S, et al. Preoperative prediction of overt hepatic encephalopathy caused by transjugular intrahepatic portosystemic shunt. Eur J Radiol 2022;154:110384.
[82] Bettinger D, Sturm L, Pfaff L, et al. Refining prediction of survival after TIPS with the novel Freiburg index of post-TIPS survival. J Hepatol 2021;74(6):1362–72.
[83] Berenguer M. Nutritional status in hepatic encephalopathy and transjugular intrahepatic portosystemic shunt – TIPS, and strategies to improve the outcomes. Acta Gastro Enterol Belg 2023;86(2):318–22.
[84] Mazumder NR, Fontana RJ. MELD 3.0 in Advanced Chronic Liver Disease. Annu Rev Med 2024;75:233–45.
[85] Tong H, Gan C, Wei B, et al. Risk factors for overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt creation in patients with liver cirrhosis. J Dig Dis 2021;22(1):31–40.
[86] Alessandria C, Gaia S, Marzano A, et al. Application of the model for end-stage liver disease score for transjugular intrahepatic portosystemic shunt in cirrhotic patients with refractory ascites and renal impairment. Eur J Gastroenterol Hepatol 2004;16(6):607–12.
[87] Allegretti AS, Ortiz G, Cui J, et al. Changes in Kidney Function After Transjugular Intrahepatic Portosystemic Shunts Versus Large-Volume Paracentesis in Cirrhosis: A Matched Cohort Analysis. Am J Kidney Dis: J Natl Kidney Found 2016;68(3):381–91.
[88] Anderson CL, Saad WEA, Kalagher SD, et al. Effect of transjugular intrahepatic portosystemic shunt placement on renal function: a 7-year, single-center experience. J Vasc Interv Radio: JVIR 2010;21(9):1370–6.
[89] Navadurong H, Thanapirom K, Wejnaruemarn S, et al. Validation of the albumin-bilirubin score for identifying decompensation risk in patients with compensated cirrhosis. World J Gastroenterol 2023;29(32):4873–82.
[90] Hiraoka A, Kumada T, Michitaka K, et al. Newly Proposed ALBI Grade and ALBI-T Score as Tools for Assessment of Hepatic Function and Prognosis in Hepatocellular Carcinoma Patients. Liver Cancer 2019;8(5):312–25.
[91] Toyoda H, Johnson PJ. The ALBI score: From liver function in patients with HCC to a general measure of liver function. JHEP Rep: Innov Hepatol 2022;4(10):100557.

[92] Wang J, Zhang Z, Yan X, et al. Albumin-Bilirubin as an accurate and simple prognostic score for chronic hepatitis B-related liver cirrhosis. Dig Liver Dis: J Ital Soc Gastroenterol Ital Assoc Study Liver 2019;51(8):1172–8.
[93] Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of Liver Function in Patients With Hepatocellular Carcinoma: A New Evidence-Based Approach—The ALBI Grade. J Clin Oncol 2015;33(6):550–8.
[94] Cai W, Zheng B, Lin X, et al. Prediction of Patient Hepatic Encephalopathy Risk with Freiburg Index of Post-TIPS Survival Score Following Transjugular Intrahepatic Portosystemic Shunts: A Retrospective Study. Int J Gen Med 2022; 15:4007–16.
[95] Verma N, Dhiman RK, Choudhury A, et al. Dynamic assessments of hepatic encephalopathy and ammonia levels predict mortality in acute-on-chronic liver failure. Hepatol Int 2021;15(4):970–82.
[96] Khattak A, Mehak Z, Ahmad H, et al. Customer churn prediction using composite deep learning technique. Sci Rep 2023;13(1):17294.
[97] Dantas Machado AC, Ramos SF, Gauglitz JM, et al. Portosystemic shunt placement reveals blood signatures for the development of hepatic encephalopathy through mass spectrometry. Nat Commun 2023;14(1):5303.
[98] Jun-Tao T, Xiao-Mei X, Yu-Xin H, et al. Construction of prediction model of cirrhosis-related hepatic encephalopathy based on machine learning algorithm. Jie Fang Jun Yi Xue Za Zhi 2021;46(4):354.
[99] Khalifa A, Obeid JS, Erno J, et al. The role of artificial intelligence in hepatology research and practice. Curr Opin Gastroenterol 2023;39(3):175–80.
[100] Mehta V. Artificial intelligence in medicine: revolutionizing healthcare for improved patient outcomes. J Med Res Innov 2023;7(2):e000292.
[101] Upadhyaya A, Mishra MK, Saxena A. User Preferences for AI-based Healthcare Apps: an Association Mining Analysis. SN Comput Sci 2024;5(5):464.
[102] Amodio P. Hepatic encephalopathy: Diagnosis and management. Liver Int 2018; 38(6):966–75.
[103] Chen F, Li J, Zhang W, et al. Retracted] Risk Factor Analysis of Hepatic Encephalopathy and the Establishment of Diagnostic Model. BioMed Res Int 2022;2022(1):3475325.
[104] Sadeghi Z, Alizadehsani R, Cifci MA, et al. A review of Explainable Artificial Intelligence in healthcare. Comput Electr Eng 2024;118:109370.
[105] Pham N, Hill V, Rauschecker A, Lui Y, et al. Critical Appraisal of Artificial Intelligence-Enabled Imaging Tools Using the Levels of Evidence System. Am J Neuroradiol 2023;44(5):21–8.
[106] Petrick N, Chen W, Delfino JG, et al. Regulatory considerations for medical imaging AI/ML devices in the United States: concepts and challenges. J Med Imaging 2023;10(5):051804.
[107] Chan CYT, Petrikat D. Strategic applications of artificial intelligence in healthcare and medicine. J Med Health Stud 2023;4(3):58–68.
[108] Toma M, Wei OC. Predictive Modeling in Medicine. Encyclopedia 2023;3(2): 590–601.
[109] Arasteh ST, Lotfinia M, Nolte T, et al. Preserving privacy in domain transfer of medical AI models comes at no performance costs: The integral role of differential privacy. Radiology 2024;6(1):e230212.
[110] Santoro E. Artificial intelligence in medicine: are we ready? Recent Progress Med 2023;114(3):142–4.
[111] Miwa T, Hanai T, Nishimura K, et al. A simple covert hepatic encephalopathy screening model based on blood biochemical parameters in patients with cirrhosis. PLoS One 2022;17(11):e0277829.
[112] Elwir S, Hal H, Veith J, et al. Radiographical findings in patients with liver cirrhosis and hepatic encephalopathy. Gastroenterol Rep 2016;4(3):221–5.
[113] Cheng S, Hu G, Jin Z, et al. Prediction of Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt Based on CT Radiomic Features of Visceral Adipose Tissue. Acad Radiol 2023;31(5):1849–61.
[114] Ronald J, Bozdogan E, Zaki IH, et al. Relative Sarcopenia With Excess Adiposity Predicts Survival After Transjugular Intrahepatic Portosystemic Shunt Creation. Am J Roentgenol 2020;214(1):200–5.
[115] Cai W, Lin H, Qi R, et al. Psoas Muscle Density Predicts Occurrences of Hepatic Encephalopathy in Patients Receiving Transjugular Intrahepatic Portosystemic Shunts within 1 year. Cardiovasc Interv Radiol 2022;45:93–101.
[116] İnce O, Önder H, Gençtürk M, et al. Machine Learning Insights: Predicting Hepatic Encephalopathy After TIPS Placement. Cardiovasc Interv Radiol 2023;46(12): 1715–25.
[117] Srinivasu PN, Sandhya N, Jhaveri RH, et al. From blackbox to explainable AI in healthcare: existing tools and case studies. Mob Inf Syst 2022;2022(1). 8167821.
[118] Das D, Ito J, Kadowaki T, et al. An interpretable machine learning model for diagnosis of Alzheimer's disease. PeerJ 2019;7:e6543.
[119] Holzinger A, Langs G, Denk H, et al. Causability and explainability of artificial intelligence in medicine. Wiley Interdiscip Rev: Data Min Knowl Discov 2019;9 (4):e1312.
[120] Zhang Y, Weng Y, Lund J. Applications of Explainable Artificial Intelligence in Diagnosis and Surgery. Diagn (Basel) 2022;12(2):237.
[121] Aldughayfiq B, Ashfaq F, Jhanjhi N, et al. Explainable AI for retinoblastoma diagnosis: interpreting deep learning models with LIME and SHAP. Diagnostics 2023;13(11):1932.
[122] Altman R. Artificial intelligence (AI) systems for interpreting complex medical datasets. Clin Pharmacol Ther 2017;101(5):585–6.
[123] Gianfrancesco MA, Tamang S, Yazdany J, et al. Potential biases in machine learning algorithms using electronic health record data. JAMA Intern Med 2018; 178(11):1544–7.
[124] Nguyen T, Dakka M, Diakiw S, et al. A novel decentralized federated learning approach to train on globally distributed, poor quality, and protected private medical data. Sci Rep 2022;12(1):8888.
[125] Russo G, Parasiliti Palumbo GA, Pennisi M, et al. Model verification tools: a computational framework for verification assessment of mechanistic agent-based models. BMC Bioinforma 2021;22(Suppl 14):626.
[126] Ong Ly C, Unnikrishnan B, Tadic T, et al. Shortcut learning in medical AI hinders generalization: method for estimating AI model generalization without external data. npj Digit Med 2024;7(1):124.
[127] Tsopra R, Fernandez X, Luchinat C, et al. A framework for validating AI in precision medicine: considerations from the European ITFoC consortium. BMC Med Inform Decis Mak 2021;21(1-14).
[128] Napoli A, White P. arXiv preprint. arXiv:2405.19461, Clust-Based Valid Splits Domain Gen 2024.
[129] Khan A, Tariq I, Khan H, et al. Lung cancer nodules detection via an adaptive boosting algorithm based on self-normalized multiview convolutional neural network. J Oncol 2022;2022(1). 5682451.
[130] Ríos-Hoyo A, Shan NL, Li A, et al. Evaluation of large language models as a diagnostic aid for complex medical cases. Front Med 2024;11:1380148.
[131] Hirosawa T, Harada Y, Yokose M, et al. Diagnostic accuracy of differential-diagnosis lists generated by generative pretrained transformer 3 chatbot for clinical vignettes with common chief complaints: a pilot study. Int J Environ Res Public Health 2023;20(4):3378.
[132] Kanjee Z, Crowe B, Rodman A. Accuracy of a generative artificial intelligence model in a complex diagnostic challenge. JAMA 2023;330(1):78–80.
[133] Meng X, Yan X, Zhang K, et al. The application of large language models in medicine: A scoping review. iScience 2024;27(5):109713.
[134] Bonnasse-Gahot L., Pallier C. fMRI predictors based on language models of increasing complexity recover brain left lateralization. arXiv preprint arXiv: 240517992.2024.
[135] Salih A., Raisi-Estabragh Z., Galazzo I.B., et al. Commentary on explainable artificial intelligence methods: SHAP and LIME. arXiv preprint arXiv:230502012. 2023.
[136] Cavusoglu D., Eryuksel O., Altinuc S. Increasing Data Diversity with Iterative Sampling to Improve Performance. arXiv preprint arXiv:211103743. 2021.
[137] Li L, Chang J, Vakanski A, et al. Uncertainty quantification in multivariable regression for material property prediction with Bayesian neural networks. Sci Rep 2024;14(1):10543.
[138] Nojima M, Tokunaga M, Nagamura F. Quantitative investigation of inappropriate regression model construction and the importance of medical statistics experts in observational medical research: a cross-sectional study. Bmj Open 2018;8(5): e021129.
[139] Kaciroti NA, Lumeng C, Parekh V, et al. A Bayesian mixture model for predicting the COVID-19 related mortality in the United States. Am J Trop Med Hyg 2021; 104(4):1484.
[140] Li X, Qin X, Huang C, et al. SUnet: A multi-organ segmentation network based on multiple attention. Comput Biol Med 2023;167:107596.
[141] Hu H, Feng Z, Lin H, et al. Gene function and cell surface protein association analysis based on single-cell multiomics data. Comput Biol Med 2023;157: 106733.
[142] Wei C, Xiang X, Zhou X, et al. Development and validation of an interpretable radiomic nomogram for severe radiation proctitis prediction in postoperative cervical cancer patients. Front Microbiol 2022;13:1090770.
[143] Liu D, Liu B, Lin T, et al. Measuring depression severity based on facial expression and body movement using deep convolutional neural network. Front Psychiatry 2022;13:1017064.
[144] Choi KJ, Jang JK, Lee SS, et al. Development and Validation of a Deep Learning System for Staging Liver Fibrosis by Using Contrast Agent-enhanced CT Images in the Liver. Radiology 2018;289(3):688–97.
[145] Qiu Q-T, Zhang J, Duan J-H, et al. Development and validation of radiomics model built by incorporating machine learning for identifying liver fibrosis and early-stage cirrhosis. Chin Med J 2020;133(22):2653–9.
[146] Chen H, Ye H, Chen F, et al. Revolutionizing Infection Risk Scoring: An Ensemble "From Weak to Strong" Deduction Strategy and Enhanced Point-of-Care Testing Tools. Adv Intell Syst 2023;5(11):2300224.
[147] Hu H, Feng Z, Lin H, et al. Modeling and analyzing single-cell multimodal data with deep parametric inference. Brief Bioinforma 2023;24(1):bbad005.
[148] Cai Z, Fan S, Sun X, et al. Novel microfluidic device for measurable residual disease detection in acute leukemia. Innovation 2023;4(3):100408.
[149] Esteva A, Robicquet A, Ramsundar B, et al. A guide to deep learning in healthcare. Nat Med 2019;25:24–9.
[150] Taylor-Weiner A, Pokkalla H, Han L, et al. A Machine Learning Approach Enables Quantitative Measurement of Liver Histology and Disease Monitoring in NASH. Hepatology 2021;74:133–47.
[151] Noureddin M. Artificial Intelligence in NASH Histology: Human Teaches a Machine for the Machine to Help Humans. Hepatology 2021;74(1):9–11.
[152] Forlano R, Mullish B, Giannakeas N, et al. High-Throughput, Machine Learning-Based Quantification of Steatosis, Inflammation, Ballooning, and Fibrosis in Biopsies From Patients With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol 2020;18(9):2081–90.
[153] Hou Y, Zhang Q, Gao F, et al. Artificial neural network-based models used for predicting 28- and 90-day mortality of patients with hepatitis B-associated acute-on-chronic liver failure. BMC Gastroenterol 2020;20:75.
[154] Wang N, Zhang P, Tapper E, et al. Automated Measurements of Muscle Mass Using Deep Learning Can Predict Clinical Outcomes in Patients With Liver Disease. Am J Gastroenterol 2020;115(8):1210–6.
[155] Gilson A, Safranek C, Huang T, et al. How Does ChatGPT Perform on the United States Medical Licensing Examination? The Implications of Large Language

Models for Medical Education and Knowledge Assessment. JMIR Med Educ 2023; 9(1)):e45312.
[156] Chakraborty C, Pal S, Bhattacharya M, et al. Overview of Chatbots with special emphasis on artificial intelligence-enabled ChatGPT in medical science. Front Artif Intell 2023;6:1237704.
[157] Zhang C, Xu J, Tang R, et al. Novel research and future prospects of artificial intelligence in cancer diagnosis and treatment. J Hematol Oncol 2023;16(1):114.
[158] Zhang Y., Liu H., Sheng B., et al. Preliminary fatty liver disease grading using general-purpose online large language models: ChatGPT-4 or Bard? Journal of Hepatology. 2023;S0168–8278(23):05293–05295.
[159] Mallio C, Sertorio A, Bernetti C, et al. Large language models for structured reporting in radiology: performance of GPT-4, ChatGPT-3.5, Perplexity and Bing. La Radiol Med 2023;128(7):808–912.
[160] Malinchoc M, Kamath P, Gordon F, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31(4):864–71.