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Artificial intelligence-based evaluation of prognosis in cirrhosis

Yinping Zhai[1†], Darong Hai[2†], Li Zeng[3†], Chenyan Lin[2], Xinru Tan[4], Zefei Mo[5], Qijia Tao[2], Wenhui Li[2], Xiaowei Xu[1], Qi Zhao[6,7*], Jianwei Shuai[7,8*] and Jingye Pan[9,10,11*]

Abstract

Cirrhosis represents a significant global health challenge, characterized by high morbidity and mortality rates that severely impact human health. Timely and precise prognostic assessments of liver cirrhosis are crucial for improving patient outcomes and reducing mortality rates as they enable physicians to identify high-risk patients and implement early interventions. This paper features a thorough literature review on the prognostic assessment of liver cirrhosis, aiming to summarize and delineate the present status and constraints associated with the application of traditional prognostic tools in clinical settings. Among these tools, the Child–Pugh and Model for End-Stage Liver Disease (MELD) scoring systems are predominantly utilized. However, their accuracy varies significantly. These systems are generally suitable for broad assessments but lack condition-specific applicability and fail to capture the risks associated with dynamic changes in patient conditions. Future research in this field is poised for deep exploration into the integration of artificial intelligence (AI) with routine clinical and multi-omics data in patients with cirrhosis. The goal is to transition from static, unimodal assessment models to dynamic, multimodal frameworks. Such advancements will not only improve the precision of prognostic tools but also facilitate personalized medicine approaches, potentially revolutionizing clinical outcomes.

Keywords Cirrhosis, Prognosis, Machine learning, Markers, Artificial intelligence

†Yinping Zhai, Darong Hai and Li Zeng have authors contributed equally to the paper as first authors.

*Correspondence:
Qi Zhao
zhaoqi@lnu.edu.cn
Jianwei Shuai
shuaijw@wiucas.ac.cn
Jingye Pan
panjingye@wzhospital.ac.cn
[1] Department of Gastroenterology Nursing Unit, Ward 192, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China
[2] The School of Nursing, Wenzhou Medical University, Wenzhou 325000, China
[3] The Second Clinical Medical College of Wenzhou Medical University, Wenzhou 325000, China
[4] The First School of Medicine, School of Information and Engineering, Wenzhou Medical University, Wenzhou 325000, China
[5] School of Biomedical Engineering, School of Ophthalmology and Optometry, Eye Hospital, Wenzhou Medical University, Wenzhou 325000, China
[6] School of Computer Science and Software Engineering, University of Science and Technology Liaoning, Anshan 114051, China
[7] Wenzhou Institute, University of Chinese Academy of Sciences, Wenzhou 325000, China
[8] Oujiang Laboratory (Zhejiang Lab for Regenerative Medicine, Vision, and Brain Health), Wenzhou 325000, China
[9] Department of Big Data in Health Science, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China
[10] Key Laboratory of Intelligent Treatment and Life Support for Critical Diseases of Zhejiang Province, Wenzhou 325000, China
[11] Zhejiang Engineering Research Center for Hospital Emergency and Process Digitization, Wenzhou 325000, China

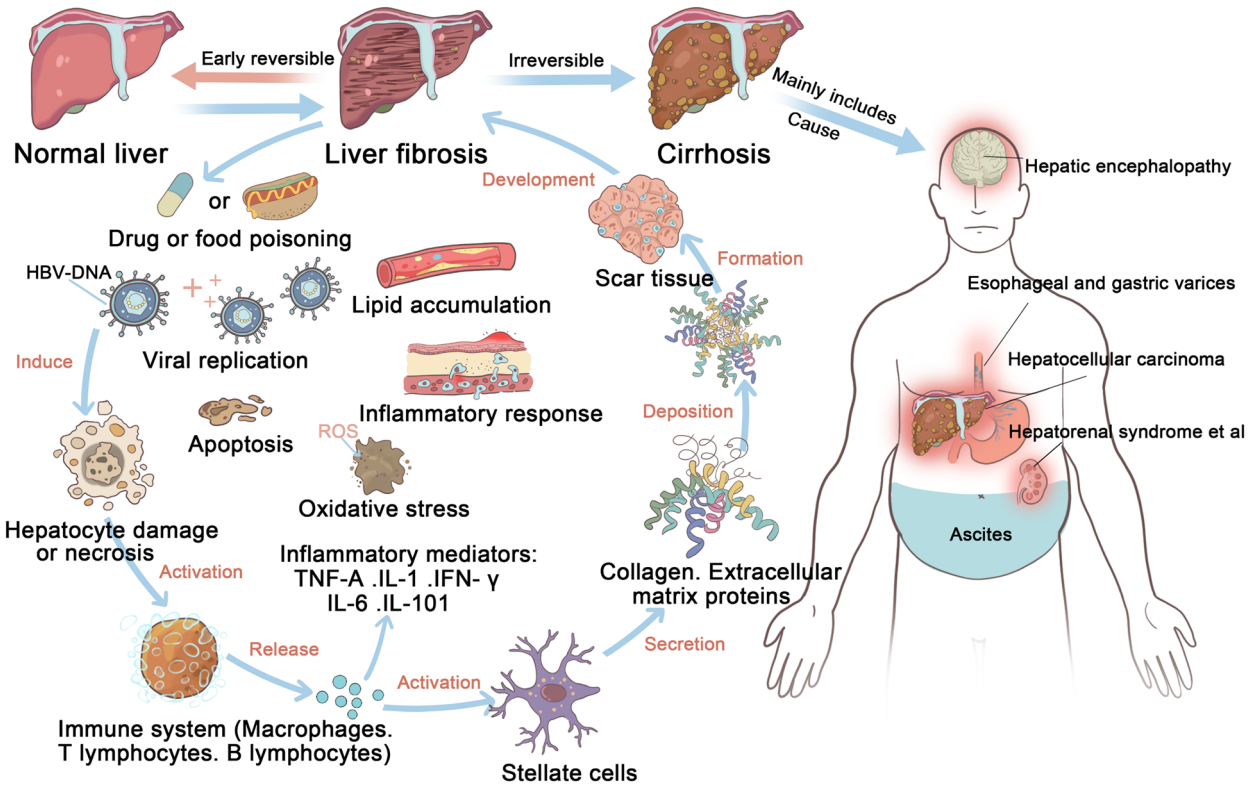

Fig. 1 Progression from healthy liver to cirrhosis and major complications. The diagram illustrates the pathogenesis of liver fibrosis due to factors such as viral replication, lipid accumulation and oxidative stress, and further outlines the progression from liver fibrosis to cirrhosis, and highlights associated complications

Introduction

Cirrhosis refers to the terminal phase of severe functional and structural impairment in the liver, attributable to various chronic liver diseases (CLD). This condition is pathologically manifested with extensive hepatocellular necrosis, fibrosis, and inflammations, culminating in the substitution of normal hepatic tissue with scar tissue, thereby precipitating hepatic dysfunction [1–3]. These exhibitions are displayed in Fig. 1. Data from the Global Burden of Disease (GBD) study revealed that, in 2019, the global prevalence of cirrhosis was approximately 169 million individuals, accompanied by roughly 1.47 million cirrhosis-related fatalities. The significant morbidity and mortality rates underscore the urgency of cirrhosis as a critical global public health concern [4]. The development and refinement of dependable tools for predicting the progression and outcomes of cirrhosis remain pivotal challenges in clinical research. This study aims to conduct a systematic review of the current global status of cirrhosis prognosis, the methodologies employed in prognostic evaluations, and recent advancements in prognostic approaches for cirrhosis. This work aims to conduct a systematic review of the current global status of cirrhosis prognosis, the methodologies employed in prognostic evaluations, and recent advancements in prognostic approaches for cirrhosis. It seeks to offer innovative perspectives and methodologies to enhance the early and precise prognosis of patients with cirrhosis.

The prognostic status of liver cirrhosis

The etiology of cirrhosis encompasses a diverse array of factors, including viral hepatitis forms (predominantly hepatitis B and C), chronic alcohol consumption, obesity, non-alcoholic fatty liver disease (NAFLD), autoimmune liver disease (ALD), and cholestatic liver diseases [5, 6]. The morbidity and mortality rates among cirrhosis patients exhibit notable variations based on the underlying etiology [4, 7] (Table 1). Globally, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections contribute to over 45% of cirrhosis cases, with an estimated 50% of cirrhosis-related deaths attributed to these infections [6]. Alcohol consumption leads to a significant rise in the incidence of alcoholic cirrhosis from 18.7% to 21.3%, resulting in a mortality rate of up to 2.5% for patients with alcohol-induced cirrhosis [4, 8, 9]. Moreover, the rising prevalence of obesity and type 2 diabetes mellitus has promoted the incidence of cirrhosis associated with NAFLD from 5.5% to 6.6% [6, 9].

Table 1 The 2019 Global Burden of Disease (GBD) study shows mortality from liver cirrhosis

	Prevalent cases	Deaths	mortality rate
Hepatitis B	316689100	331300	0.001046
Hepatitis C	112371500	395000	0.003515
NAFLD	1235652900	134200	0.000109
Alcohol use	14837900	372000	0.025071
Other causes	11409800	239500	0.020991

Cirrhosis is typically categorized into two distinct phases, the compensated and decompensated stages, each exhibiting substantial divergence in prognosis [10, 11]. Within the compensated stage of cirrhosis, the median length of survival can reach more than 15 years. However, upon transitioning into the decompensated stage, the median length of survival shrinks to a mere 1.5 years, spanning a range of 2 to 4 years [12]. For instance, the 5-year survival rate of patients with HBV-related cirrhosis in the compensated stage ranges from 80 to 85%, significantly reducing to 14%-35% upon progression to the decompensated stage [13]. Patients transitioning into the decompensated stage often face a spectrum of complications, including gastroesophageal variceal rupture and hemorrhage, ascites, hepatic encephalopathy (HE), and hepatocellular carcinoma (HCC) [14]. The repercussions of each complication on prognosis vary and frequently contribute to increased mortality rates [11, 15–17]. Acute bleeding stemming from the rupture of gastroesophageal varices corresponds to a mortality rate of 15–20% [18]. Individuals with significant ascites (classified as grades 2 or 3) exhibit a mere 30% 5-year survival rate [10]. Those with refractory ascites confront a one-year mortality rate exceeding 20% [19]. HCC emerges as the predominant form of liver cancer, attributed to a minimum of 780,000 annual deaths, with cirrhosis serving as a primary risk factor for its development [20–22]. Additionally, HE has sustained persistently high mortality rates over the preceding decades [23, 24]. A survey revealed that the mortality rate among individuals with HCC had soared to 1.2% by the conclusion of the prior decade. A study pointed out that the median survival time of adult patients with cirrhosis and hepatic encephalopathy in the United States is only 0.92 years [5]. The sharp drop in the survival rate of patients with decompensated cirrhosis highlights the need for accurate prognostic assessment and early intervention, which is crucial to improving long-term survival.

Prognosis assessment of patients with liver cirrhosis is a key part of clinical management and relies on a series of scoring systems such as the Child–Pugh and MELD scores. A deeper understanding of the use and limitations of these assessment tools is the key and basis for accurately assessing patient prognosis, guiding clinical decision-making, and improving prognosis [17, 25–27]. Several reviews have extensively discussed research progress in prognostic assessment for cirrhosis. For instance, Gülcicegi et al. described novel concepts and viewpoints regarding the definition and classification of decompensated cirrhosis, outlined the clinical applications of emerging predictive scoring systems such as CLIF Consortium Acute Decompensation (CLIF-C AD) and Chronic Liver Failure Acute-on-Chronic Liver Failure (CLIF-ACLF) scores, Early Prediction of Decompensation (EPOD) score, and albumin-bilirubin (ALBI) score, and discussed non-invasive methods for assessing portal hypertension and the application of new biomarkers in early identification of cirrhotic patients at risk of acute decompensation [28]. Valainathan et al. compared the differences and similarities between six prognostic scoring systems for cirrhosis severity and prognosis, including Child–Pugh score, Model for End-Stage Liver Disease (MELD) score, CLIF-C-AD score for patients in acute decompensation stage of cirrhosis, Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure (Clif-C-ACLF), American Association for Respiratory Care (AARC), and North American Consortium for the Study of End-Stage Liver Disease (NASCELD)-ACLF scores proposed by European, Asian, and North American societies for more severe patients. They discussed the validation and limitations of these systems and indicated that the predictive value of these systems for mortality could still be improved as their Receiver Operating Characteristic (ROC) curve areas do not exceed 0.8, suggesting that incorporating biomarkers reflecting the pathophysiology of acute decompensation of cirrhosis into scoring systems may help achieve this goal [29]. In summary, these review articles have discussed the clinical application benefits and limitations of commonly used clinical tools for prognostic assessment of cirrhosis, and they have pointed out that a new perspective for improving these scoring systems is the application of novel biomarkers related to cirrhosis. Our work not only discusses the historical development, clinical application, and limitations of commonly used clinical assessment systems (Child–Pugh score and MELD score) for cirrhosis prognosis assessment, but also from the perspective of the application of advanced technology, elucidates the clinical efficacy of newly discovered immunobiochemical markers, microbiological markers, microRNA (miRNA) markers and ultrasound (US) imaging markers closely related to cirrhosis prognosis in recent years. Most importantly, this

review consolidates the literature on the application of artificial intelligence (AI) technology in cirrhosis prognosis assessment, indicating another broad area for future development in cirrhosis prognosis assessment. Refer to Fig. 2 for additional details. The fusion of AI and medicine is an inevitable trend in the future. In cirrhosis prognosis assessment, future research should focus on dynamic data processing and multimodal model construction to achieve real-time early warning assessment of cirrhosis prognosis, promote further development of precision medicine, and contribute to changing the high mortality rate of cirrhosis.

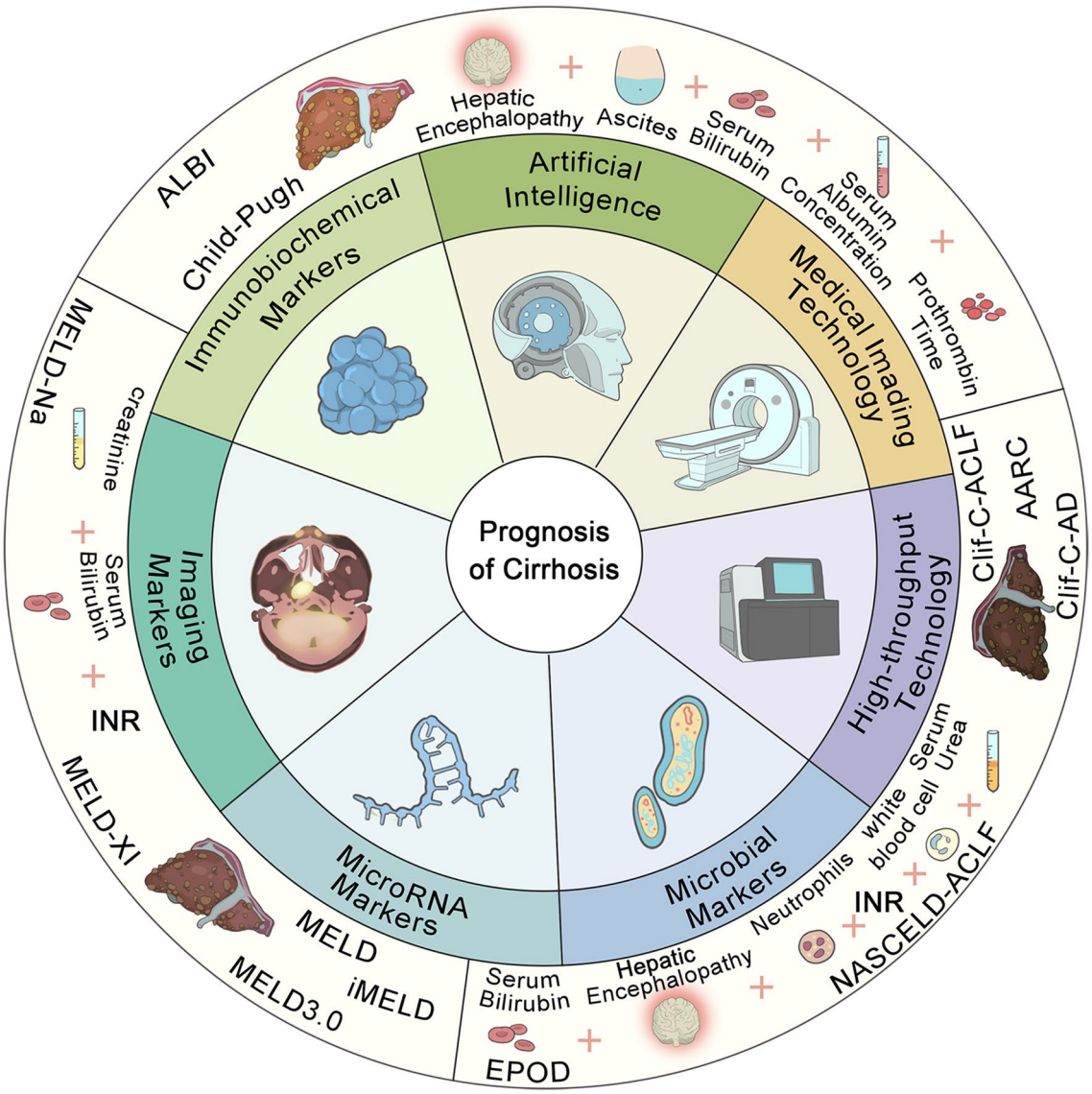

Fig. 2 Assessment tools, markers, and techniques for cirrhosis prognosis. The figure summarizes a comprehensive overview of the progress in research on prognostic assessment tools for cirrhosis. With the rapid evolution of science and technology, the integration of advanced high-throughput sequencing, imaging techniques, and (AI) has proven instrumental in identifying in validating new microbial biomarkers and miRNA markers, as well as immunobiochemical and imaging markers, which are essential for the prognostic evaluation of cirrhosis. Along with these advancements, the prognostic assessment tools for cirrhosis have been continuously refined and updated. The current tools are primarily divided into two main categories and three systems based on their applicability to either the stable phase or the decompensated phase of cirrhosis. For stable cirrhosis, the Child–Pugh score and MELD score serve as the foundational assessment systems; for decompensated cirrhosis, the assessment is mainly based on the CLIF-C Acute-on-Chronic Liver Failure score

Traditional methods of prognostic assessment in cirrhosis

Traditional tools for prognostic assessment in cirrhosis can be divided into two categories: those targeting the early or stable stage, and those targeting the decompensated stage. For early or stable cirrhosis, commonly used traditional scoring systems include the Child–Pugh scoring system and the MELD and its enhanced versions. In the decompensated stage, prognostic assessment systems for cirrhosis are based on the machine-learning-enhanced version of the Clif-C-ACLF scoring system.

Traditional scoring systems for early or stable cirrhosis

The child–pugh scoring system: an empirical clinical assessment

History of the child–pugh scoring system In 1964, surgeons Child and Turcotte introduced the Child-Turcotte system, an index designed to evaluate liver function among cirrhosis patients [30]. Subsequently, Pugh and collaborators revamped the Child-Turcotte classification in 1973, refining it based on clinical insights. The revised system encompassed five pivotal indicators: albumin levels, coagulation status, bilirubin levels, presence of ascites, and HE. Each indicator is assigned a score corresponding to its severity, with liver function categorized into three grades based on the total score: A (5–6), B (7–9), and C (10–15), denoting good, moderate, and severely impaired liver function, respectively. This classification hinges on the cumulative point allocation for each indicator, reflecting the comprehensive evaluation of liver function in cirrhosis patients [31].

Limitations of the child–pugh scoring system The Child–Pugh scoring system has traditionally served as a pivotal tool in evaluating disease severity among cirrhosis patients, playing a significant role in survival assessment and selection of therapeutic approaches [31–35]. However, the subjective nature of ascites and HE grading within the Child–Pugh scoring system, along with the utilization of cutoff points for the albumin level, International Normalized Ratio (INR), and bilirubin level calculations, raised concerns regarding its grading accuracy and discriminatory capacity in certain studies [32]. Additionally, the Child–Pugh scoring system's prognostic precision is challenged by its inherent limitations, such as the failure to incorporate renal function, the inability to distinguish between cirrhosis etiologies, considerable individual variability across patients within the ABC grading levels, and the lack of a comprehensive evaluation of hepatic metabolic function [36]. Consequently, numerous research teams sought to further refine prognostic assessments for cirrhosis patients following the Child–Pugh classification, aiming to enhance the precision and efficacy of prognostic evaluations in cirrhosis management [37–40].

Developments of the child–pugh scoring system With the advancements of statistical methodologies, researchers endeavored to enhance the Child–Pugh scoring system by conducting in-depth statistical analyses on extensive clinical datasets with the goal to bolster the accuracy of prognostic evaluations for patients grappling with cirrhosis [41–44]. In 2015, Johnson and colleagues leveraged data from 1,313 individuals with HCC to create an ALBI scoring model [45]. This model exhibited superior predictive capabilities in gauging the prognosis of HCC patients compared to the Child–Pugh scoring system, a finding corroborated by subsequent investigations [46, 47]. The Japanese Society of Liver Diseases integrated ALBI scoring into their HCC therapeutic protocols [48]. Despite these advancements, a follow-up research team revealed suboptimal predictive performance in long-term prognosis with ALBI, indicating the necessity for continued refinement in accuracy. In a study conducted by Hiraoka and colleagues, the modified Child–Pugh prognostic accuracy outperformed that of ALBI, emphasizing the ongoing quest for enhanced prognostic tools in cirrhosis management [49].

The MELD and its improved scoring system: quantitative evaluation system

History of the MELD scoring system In 2000, Kamath and colleagues introduced the MELD scoring system to prognosticate the near-term mortality risk in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) surgery, predicating on a quantitative evaluation of laboratory parameters [50]. The current version of the MELD scoring system comprises three primary metrics: creatinine level, total bilirubin level, and the INR. A higher score is indicative of increased severity of hepatic disease, although the precise methodology of calculations may exhibit variations contingent on regional and institutional guidelines within the healthcare sector [51]. In subsequent studies conducted by Papatheodoridis and Botta et al. the MELD score consistently demonstrated enhanced accuracy compared to the Child–Pugh scoring system in predicting short-term survival rates for individuals with cirrhosis [52, 53].

Limitations of the MELD scoring system Nevertheless, the MELD score is not devoid of limitations. Observations indicate that cirrhotic patients are afflicted with spontaneous bacterial peritonitis (SBP) or bacterial infections (BA) exhibit a mortality rate higher than that anticipated by the MELD score predictions [54]. Additionally,

discrepancies arise when associating the low MELD scores with a concurrent high mortality rate among cirrhotic patients with severe ascites [19]. Some research findings even suggested that the predictive accuracy of the MELD scoring system falls short when compared to the Child–Pugh scoring system in forecasting 3- and 6-month mortality rates post-TIPS procedures. Specifically, the 3- and 6-month area under the curve (AUC) values were reported as 0.706/0.779 and 0.692/0.753, respectively, indicating a lesser degree of precision in prognostication when employing the MELD scoring system [50].

Developments of the MELD scoring system In response to the predictive limitations of the MELD score in specific application scenarios, researchers proposed several improved versions, such as MELD with Serum Sodium (MELD-Na), MELD-XI, integrated MELD (iMELD), and MELD3.0 [55–58].

In 2006, Scott W. Bigginsa et al. proposed the MELD-Na model, which incorporates serum sodium (Na) into the MELD score, through a prospective multicenter study that demonstrated that the MELD-Na model provided a more accurate prediction of survival than MELD alone [56]. Based on its improved accuracy, the Organ Procurement and Transplantation Network (OPTN) included it as a prioritization criterion for allocation to liver transplantation in 2016 [59]. The European 2020 study further confirmed the superiority of MELD-Na in predicting 90-day mortality with a c-index of 0.847, significantly better than conventional MELD [60]. MELD is a good predictor of short-term mortality in cirrhosis, but when anticoagulation therapy artificially elevates the International Normalized Ratio (INR), MELD may overestimate risk. To address this issue, in 2006, Douglas M constructed the MELD-XI, which includes only two biochemical markers, creatinine and total bilirubin, but substituting the MELD with the MELD-XI when evaluating patients on oral anticoagulant therapy allows for a more accurate assessment of risk and a more rational assignment of "highest priority for LT" [57]. In 2018, Wernly et al. showed that MELD-XI is equally clinically valuable in predicting mortality in patients with severe cirrhosis [61]. iMELD, which combines serum sodium and age, significantly outperformed the original MELD in predicting 12-month mortality in patients with cirrhosis: the AUROC increased by 13.4%. The likelihood ratio statistic increased from 23.5 to 48.2, highlighting the accuracy of iMELD in predicting mortality [58]. In 2015, in a study of cirrhotic patients with acute-on-chronic liver failure (ACLF), the iMELD score predicted 28-day mortality in ACLF patients better than several other prognostic models with the highest area under the operating characteristic curve (AUROC = 0.787) [62]. To further optimize the fitting of the MELD score, W. Ray Kim's team introduced MELD 3.0 in 2021, which added two parameters, sex and serum albumin, and revised the weights of each parameter to account for the interactions between albumin and creatinine and bilirubin and sodium. The results of the study showed that MELD 3.0 provided a more accurate prediction of mortality than MELDNa, with an agreement statistic (AUC) value of 0.869, while incorporating and addressing the determinants of waiting list outcomes, including gender differences [55].

The availability of these improved versions reflects the ongoing drive to improve the predictive accuracy and clinical utility of the MELD scoring system. With the continued discovery of biomarkers, clinical features and genomic information, we expect the MELD Scoring System to be further optimized to provide cirrhotic patients with more personalized and precise treatment strategies to prolong survival and improve quality of life.

Conventional scoring systems for the decompensated stage of cirrhosis

The loss of compensation serves as a primary indicator of disease progression in cirrhosis patients. Timely identification of the transition from compensated cirrhosis to decompensated status holds the potential to facilitate targeted therapeutic interventions, thereby potentially extending life expectancy. Liver failure, a severe complication of decompensated cirrhosis, often represents a chronic and progressive process that can precipitate a rapid decline in liver function in response to specific triggers. It does not merely delineate acute or chronic liver failure but rather embodies an interplay between the two conditions. Given the swift and dynamic nature of liver failure, prompt and agile assessment and management protocols are imperative. Traditional cirrhosis scoring systems, such as the Child–Pugh and MELD scores, predominantly focus on evaluating disease severity and patient prognosis in chronic cirrhosis cases, thereby falling short in fulfilling the exigencies of acute assessments and interventions [63–66]. Hence, the concept of ACLF has emerged, accompanied by refined scoring criteria that are specifically designed for assessing cirrhotic decompensation [67–70].

For patients experiencing rapid decompensation of cirrhosis, Jalan's team developed and validated the CLIF-C AD score based on the CANONIC study database. Age, serum sodium levels, leukocyte count, creatinine levels, and INR emerged as the most reliable predictors of mortality. In comparison to the Child–Pugh, MELD, and MELD-Na scoring systems, the CLIF-C AD score exhibited enhanced accuracy in predicting mortality, as evidenced by a superior C-index. The predictive capacity of the CLIF-C AD score for 3-month mortality displayed

incremental improvements when utilizing data from days 2, 3–7, and 8–15, resulting in C-index values of 0.72, 0.75, and 0.77, respectively [71]. While the CLIF-C AD score plays a pivotal role in mortality prediction and prognosis enhancement, a considerable proportion of prediction errors were observed within the cohort in which it was developed (26% for 90-day mortality). These observations underscore the ongoing necessity for additional studies and tools to refine prognostic prediction in cases of acute decompensation in cirrhosis.

For patients facing more severe liver failure, distinct scoring systems were introduced by the European, Asian, and North American medical communities, known as the Clif-C-ACLF, AARC score, and NASCELD-ACLF, respectively. The Clif-C-ACLF score represents an ACLF-specific prognostic tool rooted in the simplified organ function assessment system, the Chronic Liver Failure Consortium Organ Failure (CLIF-C OF) score. This score amalgamates age and white blood cell counts to formulate a comprehensive prognostic metric. While the inclusion of multiple clinical variables and biochemical indicators renders the robustness and comprehensiveness of Clif-C-ACLF score, the complexity of its calculation hampers its widespread clinical utility [72]. Subsequently, the relatively efficient AARC score was developed, incorporating predictors such as total bilirubin, HE, INR, serum creatinine, and serum lactate [73]. Furthermore, the NACSELD introduced the NACSELD-ACLF score, a practical bedside tool for predicting short-term survival in individuals with decompensated cirrhosis, drawing insights from a multicenter dataset [74]. While each of these scoring systems has made distinct contributions to the prognostic assessment of ACLF patients, they are limited in specific contexts of application. Many studies are constrained to limited sample sizes, highlighting the imperative for large-scale, multicenter trials to further elucidate the efficacy and applicability of these scoring systems [75–77].

The management of the decompensated stage of liver cirrhosis poses significant challenges in both treatment and assessment. Early detection of decompensated cirrhosis in patients holds promise in guiding physicians to implement timely interventions aimed at slowing disease progression, reducing complications, extending the length of survival, and enhancing patients quality of life [7, 78, 79]. Thus, there is an urgent demand for the development of predictive assessment models for decompensated cirrhosis. In 2022, Annika R. P. Schneider and colleagues identified key predictors designed an innovative early prognostic scoring system of clinical decompensation, called the EPOD score. The scoring metrics, incorporating platelet count, albumin levels, and bilirubin concentration, were developed with Cox regression analysis. The EPOD score demonstrated superior predictive performance compared to the established MELD and Child–Pugh scores in forecasting decompensation. Notably, the EPOD score exhibited the capability to predict the 3-year probability of decompensation, illustrating its potential as a valuable tool for early prognostication in cirrhosis management [80].

Limitations of prognostic assessment tools for liver cirrhosis and research perspectives

The Child–Pugh and MELD scoring systems are widely employed for prognostic evaluation in liver cirrhosis, encompassing four key biochemical markers, albumin level, INR, serum bilirubin level, and creatinine level, and two clinical diagnostics, ascites, and HE [31, 51]. Specific applications are shown in Table 2. According to extensive practical experience at home and abroad, the Child–Pugh and MELD scoring systems have limitations in terms of accuracy and application scenarios when determining the prognosis of liver cirrhosis [19, 44, 45, 50, 54, 81]. In instances of decompensated cirrhosis characterized by significant liver function impairment and numerous complications, the prognostication process becomes markedly more intricate compared to chronic cirrhosis. Consequently, a more comprehensive consideration of severe biochemical metrics and clinical indices becomes imperative for accurate prognostic assessments in decompensated cirrhosis. Both the EPOD score, the CLIF-C AD score, and a number of scores related to patients with ACLF have limitations in practical clinical application. First, the calculation process of these scoring systems is relatively complex and involves multiple parameters. For example, the MELD score includes indicators such as serum bilirubin, INR, and serum creatinine. This complexity can make it difficult to quickly obtain a score without calculation tools or software [82, 83]. Second, these scoring systems have limited applicability. For example, the MELD score was originally developed to predict short-term survival in liver transplant candidates and may not be appropriate for assessing long-term prognosis in patients with non-transplantable cirrhosis [84]. Another example is the APASL AARC score, which may not be fully validated for use in non-Asian populations [85]. Patients' conditions are dynamic, and some scoring systems are more time-dependent, such as the I-ACLF scoring system proposed by NACSELD, which emphasizes the appearance of acute liver injury within a short period of time (e.g., within 4 weeks) [86]. This means that patients may require frequent assessments to capture changes in their condition, which may be impractical in resource-limited settings. Although these scoring systems are designed to improve the accuracy of prognostic assessment, they may not fully

Table 2 Child–Pugh and MELD series scoring systems

Scoring tools, references	Application indicators	Applicable stage	Formula	Target population
Child-Pugh [31, 34]	Serum albumin, INR, serum bilirubin, ascites, HE	The entire period of liver cirrhosis (compensated and decompensated)	Child–Pugh = ALS + INR level score + SBS + AS + HE scores	Cirrhosis
ALBI [44, 45]	Serum bilirubin, serum albumin	The entire period of liver cirrhosis (compensated and decompensated)	ALBI = (log10 B × 0.66) + (A × − 0.085)	HCC
MELD [36, 50–52]	Serum creatinine, total bilirubin, INR	Decompensated liver cirrhosis	MELD = 3.78 × ln [SB (mg/dL)] + 11.2 × ln [INR] + 9.57 × ln [SC (mg/dL)] + 6.43	Assessment of risk in cirrhotic patients preparing for elective TIPS procedures, prioritization classification for liver transplantation
MELD-Na [56, 59, 60]	Creatinine, total bilirubin, INR, serum sodium	Decompensated liver cirrhosis	MELD-Na = MELD—[0.025 × MELD × (140—Na)] + 140	Prioritization classification for liver transplantation
MELD-XI [57, 61]	Creatinine, total bilirubin	Decompensated liver cirrhosis	MELD-XI = 5.11 × ln (SC [mg/dL]) + 11.76 × ln (SB [mg/dL]) + 9.4	Cardiac complications in cirrhotic patients without anticoagulation therapy
Imeld [58, 62]	Serum creatinine, total bilirubin, INR, serum albumin, age	The entire period of liver cirrhosis (compensated and decompensated)	iMELD = MELD + (0.3 × age)—(0.7 × A) + 100	Cirrhosis
MELD 3.0 [55]	Serum creatinine, total bilirubin, INR, female, serum albumin	The entire period of liver cirrhosis (compensated and decompensated)	MELD 3.0 = 1.33 (if female) + 4.56 × loge (B) + 0.82 × (137—Na)—0.24 × (137—Na) × loge (B) + 9.09 × loge (INR) + 11.14 × loge (C) + 1.85 × (3.5 -A)—1.83 × (3.5—A) × loge (C) + 6	Prioritization classification for liver Transplantation, Increased weighting for female patients

ALBI albumin-bilirubin, *MELD* Model for End-Stage Liver Disease, *ALS* albumin level score, *INR* international normalized ratio, *SBS* serum bilirubin score, *AS* ascites score, *HE* hepatic encephalopathy, *SB* serum bilirubin, *SC* serum creatinine, *C* creatinine, *B* bilirubin, *A* albumin, *HCC* hepatocellular carcinoma, *TIPS* transjugular intrahepatic portosystemic shunt

capture individual differences and complex clinical situations, limiting the improvement in predictive accuracy and expansion of their use [87]. Future research initiatives should prioritize further model validation and optimization to enhance generalizability and accuracy in multicenter and large-sample clinical validations. Moreover, efforts to amalgamate the strengths of diverse scoring systems to formulate a more comprehensive and precise prognostic metric are essential. Leveraging advanced technologies like machine learning offers opportunities to explore additional biomarkers and predictors, which could potentially enhance the predictive efficacy and stability of scoring systems. In response to these challenges, the research team is dedicated to identifying biomarkers associated with cirrhosis prognosis, advancing the development and validation of more refined cirrhosis prognostic models. Emerging evidence suggests the association of immunobiochemical markers, microorganisms, genes, miRNAs, and US imaging data with cirrhosis prognosis [88–92].

Application of new biochemical markers in the prognosis assessment of liver cirrhosis

In recent years, in addition to the markers used in the Child–Pugh and MELD scoring systems, an increasing number of new biomarkers closely related to the prognosis of liver cirrhosis have been discovered [93–95].

Biochemical marker

Markers such as blood ammonia, antithrombin III, serum CysC and uNAG have been shown in various studies to be independent predictors of death in cirrhosis [96–98]. In the MELD-Na scoring system, blood sodium is a key indicator, but Sumarsono's research suggests that blood chloride may be a more accurate prognostic indicator [99]. In the event of acute exacerbation of cirrhosis, studies have found that serum total cortisol (t-Cort) and effective albumin concentration (eAlb) are independent predictors of decompensation progression and death in patients with ACLF [100, 101]. The above markers can be measured in a general clinical laboratory, which has the advantages of timely detection and low cost, and is conducive to large-scale verification.

The application of molecular biology techniques has brought more new biomarkers for the study of the prognosis of liver cirrhosis. Gambino's research revealed the utility of urinary neutrophil gelatinase-associated lipocalin (uNGAL) as a reliable biomarker of acute kidney injury (AKI) in cirrhosis, indicating significant prognostic value when quantified through enzyme-linked immunosorbent assessment [102]. Additionally, investigations demonstrated the prognostic significance of Liver-type Fatty Acid Binding Protein (L-FABP) in urine for patients with decompensated cirrhosis, reflecting its prognostic utility [103]. The Zanetto's team discovered the link between Presepsin (PSP) levels and the development of acute decompensated cirrhosis, providing insights into disease progression [104]. Zhang et al. demonstrated key associations between numerous plasma metabolites and 90-day mortality in ACLF cases, as well as pre-ACLF scenarios in non-ACLF individuals [105]. The combination of high-throughput proteomics and machine learning accelerates the efficiency of protein extraction and analysis [106]. Based on this, the Richards team identified 12 protein markers associated with the hepatic venous pressure gradient (HVPG) response in a single step [107]. These findings not only advance our understanding of the mechanism of cirrhosis, but also lay the research foundation for improving the accuracy of prognostic assessment. The above studies are summarized in Table 3.

Prognostic modeling based on novel markers

In the field of cirrhosis treatment, predicting a patient's survival and mortality rate is the key to achieving precision medicine. In recent years, with the discovery of biomarkers and advances in computer technology, a variety of prognostic scoring models have been proposed to improve the accuracy of cirrhosis prognosis assessment.Two prognostic models were developed using metabolites 4-hydroxy-3-methoxyphenyl diol sulfate, hexanoyl carnitine, and D-galacturonic acid, which demonstrated robust accuracy in forecasting mortality across different time intervals following the admission of patients with decompensated cirrhosis. Importantly, these models surpassed the predictive capabilities of the MELD-Na scoring system in cases of acutely exacerbated chronic liver failure [108]. The research conducted by Cagnin et al. verified the high predicative accuracy of their model for mortality at specified intervals following hospital admission in patients with cirrhotic HCC [109]. Meanwhile, Gao et al. improved prognostic models for patients with cirrhosis of elevated lactate levels [110]. Leveraging high-throughput proteomics and machine learning techniques, Niu's team succeeded in identifying 5,515 proteins and evaluating 22 machine learning models. This rigorous evaluation process led to the selection of an optimal model exhibiting exceptional predictive capabilities, as evidenced by AUC scores of 0.92 for liver fibrosis in cases of alcohol-related liver disease, 0.87 for mild inflammation, and 0.7982 for mortality [111]. These statistical models designed for specific cirrhosis scenarios, particularly in decompensated stages and conditions marked by hyperlactatemia, highlights the promising future for establishing personalized prognostic models for patients at various

Table 3 New biochemical markers in the prognosis assessment of liver cirrhosis

Biomarker	First author, references	Study type	Sample source	Detection method	Statistical methods	Target population
Plasma AT-III	Suda et al. [96]	A retrospective study	Blood	Blood test	ROC analysis	Cirrhosis with PVT
Serum CysC and uNAG	Kim et al. [97]	Prospective observational studies	Blood and urine	Blood and urine tests	Multivariate analysis	Patients with AKI in decompensated cirrhosis
Blood ammonia	Tranah et al. [98]	A retrospective study	Blood	Blood test	Random forest model	Complications of cirrhosis
Blood chloride	Sumarsono et al. [99]	Retrospective cohort study	Blood	Blood test	Kaplan–Meier analysis and multivariate Cox proportional risk modeling	Decompensated cirrhosis
t-Cort	Hartl et al. [101]	Prospective observational studies	Blood	Blood test	Multivariate Cox proportional risk model	Advanced CLD
eAlb	Baldassarre et al. [100]	Observational studies	Blood	Blood test	Kaplan–Meier analysis and multivariate Cox proportional risk models	Decompensated cirrhosis
uNGAL	Gambino et al. [102]	Prospective observational studies	Urine	ELISA	Competitive risk proportional risk Model	Patients with acute AKI in decompensated cirrhosis
L-FABP (Urine)	Juanola et al [103]	Prospective cohort study	Blood and Urine	ELISA	Multivariate analysis	Decompensated cirrhosis
PSP	Zanetto et al. [104]	Prospective study cohort study	Blood	ELISA	Multivariate Cox model	Acute decompensated cirrhosis
Metabolite	Zhang et al. [105]	Prospective study cohort study	Blood	Liquid chromatography-ass spectrometry testing	Traditional statistics machine learning	ACLF
12 proteins	Richards et al. [107]	Cohort study	Blood	High-throughput proteomics	Machine learning	Predicting response to HVPGs in cirrhotic patients with HCV

ROC receiver operating characteristic, *AT* antithrombin, *PVT* portal vein thrombosis, *CysC* serum cystatin C, *uNAG* urinary N-acetyl-β-D-glucosaminidase, *AKI* acute kidney injury, *t-Cort* total cortisol, *CLD* chronic liver disease, *eAlb* effective albumin concentration, *ELISA* enzyme-linked immunosorbent assay, *uNGAL* urinary neutrophil gelatinase-associated lipocalin, *L-FABP* liver-type fatty acid binding protein, *PSP* presepsin, *ACLF* acute-on-chronic liver failure, *HVPG* hepatic venous pressure gradient, *HCV* hepatitis C virus

stages of disease progression. Advancements in molecular biology and the application of sophisticated statistical methodologies are instrumental in refining prognostic assessments for cirrhosis patients, ultimately customizing treatment plans and improving outcomes on an individual level.

Application of microbial markers in the prognosis assessment of liver cirrhosis

In recent years, there has been a growing focus on examining the relationship between microorganisms and cirrhosis, particularly exploring the impacts of BAs and the gut-hepatic axis. [91–93]

Microbial markers

Studies have exhibited the notable increase in Enterobacteriaceae (potentially pathogenic bacteria) abundance in cirrhosis patients compared to the general population [112, 113]. Moreover, gut microbial dysbiosis in cirrhotic patients, primarily characterized by bacterial translocation due to small intestinal bacterial overgrowth (SIBO), emerges as a critical factor in cirrhosis complications and serves as an independent predictor of mortality in cirrhosis [114, 115]. Apart from intestinal bacteria, the involvement of other microbiomes has also demonstrated relevance in cirrhosis prognosis. For instance, Kim et al. established a correlation between multi-drug resistant (MDR) colonization or infection and decreased graft-free survival in cirrhotic patients. This association is particularly pronounced among critically ill cirrhotic

patients, where MDR colonization or infection correlates with a worsened prognosis [116]. Collectively, these studies evinced the potential of microbial biomarkers as prognostic tools in cirrhosis, paving the way for developing therapeutic strategies that target specific microbiota.

Application of gene sequencing technology

As gene sequencing technologies become more accessible, Solé's team conducted an analysis of the microbial population in fecal samples from cirrhotic patients utilizing macro-genomic second-generation sequencing (mNGS). Their findings revealed correlations among alterations in the gut microbiome, MELD and Child–Pugh scores, and complications such as HE and infections, facilitating the prediction of 3-month survival in patients with liver cirrhosis [91]. Concurrently, Li et al. employed mNGS to detect non-hepatitis virus in the plasma of patients during the acute decompensated phase of cirrhosis [117]. In 2023, Jinato et al. used the MO BIO PowerFecal DNA Isolation Kit (Qiagen) to extract genomic DNA from fecal samples of patients with cirrhosis and performed metagenomic sequencing. The results showed that the relative abundance of bacteriophages associated with Streptococcus, Bacteroides and Lactobacillus was higher, which was associated with the development of cognitive dysfunction in patients. These findings may help explore bacteriophages as a treatment option that affects MHE in liver cirrhosis [118]. By accurately capturing the subtle changes in the interaction between the microbial community and the host, the application of genetic sequencing technology in microbial analysis and research has provided new biomarkers and assessment methods for the prognosis of liver cirrhosis, significantly improving the accuracy of prognostic judgments and the practicality of clinical practice.

MiRNA markers in the prognosis of liver cirrhosis

Exosomal miRNAs as emerging biomarkers have shown significant potential for use in cancers such as breast cancer, rectal cancer and lung cancer. As research on exosomes deepens, more evidence is emerging to support their use in the prognostic assessment of liver cirrhosis [119–122]. Exosomes are nanoscale vesicles secreted by cells that can carry multiple biologically active molecules, including proteins, miRNAs and lipids [123–126]. These components play an important role in fibrosis, inflammatory response or apoptosis of liver cells [127–133].

MiRNA markers

Rodrigues et al. found that specific miRNAs, such as hsa-miR-21-5p, are key inducers of progression from simple steatosis to non-alcoholic steatohepatitis (NASH) and NASH-related hepatocellular carcinoma in the liver [134]. In addition, miR-218-5p and miR-301a-3p play important roles in the process of liver fibrosis [135, 136], while exosomal miR-21 and miR-1247-3p also play key roles in the progression of cirrhosis-associated hepatocellular carcinoma (HCC) [137, 138]. Animal models can recapitulate various aspects of human pathogenesis, thereby advancing our understanding of the pathogenesis and progression of cirrhosis. However, no single model can encompass all clinical aspects of human cirrhosis, and each model has its own specific characteristics in terms of the nature of pathological appearance [134, 139], the geographic distribution of fibrosis, and its evolution [135, 136]. Such limitations make the complementary use of patient-derived miRNA research an inevitable trend for future research [137, 138].

In experiments on tissue samples, Amaral et al. found that the levels of miR-34a, miR-122 and miR-885-5p were significantly higher in patients with cirrhosis, while miR-21 was associated with patient survival [139]. Other studies have shown that miR-181b-5p can predict the occurrence of ascites [140], that the expression of miR-1290 and miR-1825 is positively correlated with the tumor size and number of HCC [88], and that even exosomal miR-122 can play a suppressive role in the proliferation of HCC. These miRNA changes reflect the pathological state of the liver, especially in patients with cirrhosis, and are closely related to the severity of the disease [141]. Exosomal miRNAs can be used not only as biomarkers to monitor disease progression, but also as indicators to evaluate the efficacy of treatment. In addition, the non-invasive collection characteristics of exosomes make them ideal biomarkers that can provide information on the health status of the liver without performing liver biopsy [142, 143], demonstrating their important clinical application value in the prognostic assessment of cirrhosis. Future research should further explore the specific mechanism and clinical translation potential to provide more effective prognostic assessment strategies for patients with cirrhosis (Refer to Table 4 for additional details on microbiological markers and miRNA markers).

Application of high-throughput qPCR technology

The application of high-throughput quantitative polymerase chain reaction (qPCR) technology has significantly expanded the scope and efficiency of analysis, which could be used as a valuable tool in the study of liver cirrhosis prognosis. Utilizing this technology, researchers have identified various miRNAs, including miR-21, miR-26, miR-376a, miR-146a, and miR-191, as indicators of the severity of liver disease and patient prognoses [144, 145]. These findings are demonstrated in two distinct studies examining patients at different stages

Table 4 Comprehensive Analysis of Microbiological and miRNA Markers in Liver Cirrhosis Prognostic Assessment

First author, references	Study type	Research object	Brochure	Detection method	Microbial marker
Efremova et al. [114]	Prospective cohort study	Cirrhosis patients	Gut microbiota	Quantitative culture	SIBO
Kim et al. [116]	Observational cohort study	Multidrug-resistant microorganisms	MDR microorganisms	Sample screening	MDR
Solé et al. [98]	Prospective cohort study	Gut Microbiome	Gut microbiome genes	mNGS	Intestinal flora
Li et al. [117]	Observational cohort study	NHV	Genome fragments of circulating microorganisms	mNGS	Non-Hepatomegaly
Jinato et al. [118]	Prospective cohort study	Gut Virome	Stool metagenomics with virome and bacteriome	mNGS	Phage
Rodrigues et al. [134]	Animal studies and clinical trials	Mouse (NAFLD)	Blood and liver tissue	qPCR	Hsa-miR-21-5p
Zhang et al. [135]	Animal and cell experiments	Mouse (HBV-ACLF)	Liver tissue	qPCR	miR-218-5p
Chen et al. [136]	Animal and cell experiments	Liver fibrosis mouse	Liver tissue	qPCR	miR-301a-3p
Cao et al. [137]	Cell experiments	HCC mice	Liver tissue	qPCR	miR-21
Fang et al. [215]	Animal experiments	HCC mice	Liver tissue	qPCR	miR-1247-3p
Amaral et al. [139]	Cross-sectional study	Stable cirrhosis patients	Blood	RT-qPCR	miR-34a miR-122 miR-885-5p miR-21
Garcia de Paredes et al. [140]	Prospective Cohort Study	Compensated cirrhosis patients	Blood	RT-qPCR	miR-181b-5p
Hassan et al. [88]	Cross-sectional study	Patients with viral hepatitis-related CLD	Blood	RT-qPCR Flow cytometry analysis	CD133/EpCAM miR-1290 miR-1825
Basu et al. [141]	Cell experiments	Human hepatoma cells	HCC cell lines HepG2 and Huh7	RT-qPCR	miR-122 inhibits proliferation of HCC cells

SIBO small intestinal bacterial overgrowth, *mNGS* macro-genomic second-generation sequencing, *MDR* Multidrug-resistant, *NHV* Non-hepatotropic virus, *NAFLD* non-alcoholic fatty liver disease, *HBV-ACLF* hepatitis B virus-associated acute-on-chronic liver failure, *HCC* hepatocellular carcinoma, *CLD* chronic liver disease, *qPCR* quantitative polymerase chain reaction

of cirrhosis. Cisilotto et al. investigated the assessment of circulating miRNAs in ACLF in patients with decompensated cirrhosis with or without ACLF and found significant dysregulation of miR-25-3p and miR-223-3p [145]; however, these results were not confirmed in the study by Blaya et al [144]. Blaya's study was dedicated to the identification of circulating miRNAs associated with the progression of cirrhosis and chronic-on-acute liver failure (ACLF). The results of unsupervised clustering and principal component analysis showed that the main difference in miRNA expression occurred in the decompensated stage, with miR-21, miR-26a and miR-376a being the most dysregulated and associated with multiple organ failure, which can be used to predict whether patients have ACLF [144]. The discrepancy between the results of these two studies may be due to a combination of factors such as study design, sample differences, complexity of biological and clinical factors, limitations in data analysis and interpretation, and experimental error and variability. Further large-scale, multicenter, standardized studies are needed to more accurately evaluate the role of these miRNAs in liver disease. Additionally, the Huang's team analyzed hepatic RNA transcript high-throughput sequencing data of liver Research and Development (RND) transcripts. Employing deep residual neural network technology, they successfully identified nine crucial immune signals associated with the HBV, offering unprecedent insights into the mechanisms of HBV-related disease [146].

The modulation of the expression of these miRNAs, which serves as biomarkers for disease progression, represents a promising therapeutic strategy to mitigate or potentially reverse the pathological progression of cirrhosis. This approach assists clinicians to monitor disease progression and treatment effectiveness, ultimately contributing to an improved prognosis for patients.

Application of US imaging markers in the prognostic assessment of cirrhotic patients

Ultrasonography, which mainly encompassing abdominal US, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) techniques, has gradually become an intrinsic component in the prognostic assessment of cirrhosis [147–149].

US/CT testing evaluation

In the initial diagnosis of decompensated cirrhosis, both US and CT exhibited high accuracy, achieving diagnostic sensitivities of 0.71 and 0.74, and specificities of 0.94 and 0.93 [150], respectively. Extensive investigation has explored the use of US or CT imaging to assess liver stiffness, steatosis, and muscle loss in patients with cirrhosis, providing valuable references for monitoring cirrhosis progression and prognosis [151–156]. However, the diagnostic efficacy of US and CT for compensated cirrhosis, particularly in patients classified under Child–Pugh Class A, remains suboptimal. The sensitivities recorded for US and CT in such cases dropped to 0.62 and 0.60, respectively [150]. This diagnostic limitation can impede timely interventions in the early stages of compensated cirrhosis, adversely affecting disease progression and prognosis. Considering that cirrhosis typically progresses gradually from a compensated to a decompensated stage, with patients in the latter often requiring repeated hospitalizations and facing increased mortality risks, early diagnosis during the compensated stage is critical [5, 17, 157].

MRI testing evaluation

In the past years, advancements in MRI techniques have shown substantial benefits for early diagnosis and prognostic assessment of liver disease [90, 158]. A multicenter study conducted in the United States demonstrated that Magnetic Resonance Elastography (MRE)-based liver stiffness measurement (LSM) could effectively predict the future progression of both compensated and decompensated phases of CLD [159]. Similarly, research by Park, Loomba, Noureddin, and Gidener, among others, corroborated the effectiveness of MRI in the early assessment of patients with NAFLD [160–163]. In the context of decompensated cirrhosis, retrospective studies have illustrated MRI's superiority in detecting HCC at earlier stages compared to US. This capacity could potentially facilitate more timely therapeutic interventions, leading to improved survival outcomes and reduced disease progression [90].

Applications of AI

The application of artificial intelligence (AI) has brought about a profound change in the prognostic assessment of liver cirrhosis. The introduction of AI technology, especially deep learning in image recognition and big data analysis, has shown great potential in improving the diagnostic accuracy and efficiency of prognostic assessment [164]. By automating the analysis of imaging data, AI has accelerated the diagnostic process, improved the consistency of results, and provided clinicians with a more reliable tool for prognostic assessment.

Deep convolutional neural networks (DCNNs), one of the most commonly used deep learning methods for cirrhosis prognosis, consist of multiple layers, including convolutional layers, activation functions (such as ReLU), pooling layers, and fully connected layers. They can process image data by simulating the operation of the human visual system, automatically extract image features, and provide technical support for cirrhosis prognosis assessment from an imaging perspective. For example, the assessment of muscle mass plays a central role in predicting the clinical outcome of cirrhosis patients, and the application of DCNN makes it possible to automatically extract muscle size from CT scans. Using the manually delineated psoas major muscle as the "truth" based on a University of Michigan reference analysis morphological cohort of 5,268 patients [165], Wang combined deep convolutional neural networks with CT scanning technology to achieve automated measurement of psoas major muscle mass. This method not only has excellent spatial overlap with manual measurements, but also significantly improves efficiency and consistency, providing a new prognostic assessment tool for clinical use. The automatically measured psoas muscle size has been shown to predict mortality in patients with cirrhosis. In 2017, Koichiro Yasaka et al. used a deep convolutional neural network (DCNN) model to analyze gadoxetic acid-enhanced hepatobiliary phase MR images, accurately identifying liver fibrosis stages and providing a new perspective for non-invasive assessment of liver cirrhosis [166]. In 2020, Yanna Liu and her team developed an intelligent model using a deep convolutional neural network to automatically detect clinically significant portal hypertension (CSPH) in patients with cirrhosis by analyzing 10,014 liver images and 899 spleen images from 679 participants who underwent CT analysis and 45,554 images from 271 participants who underwent MR analysis. The model demonstrated a high AUC of 0.940 in an MR image-based test, a result that not only demonstrates the potential of DCNNs for non-invasive detection of CSPH, but also highlights its importance in improving the speed and accuracy of diagnosis. However, the general applicability of this study is limited due to the invasive nature and cost of HVPG measurements, as well as the difficulty of performing them in early stage patients. Future studies need to validate

these models in a wider range of patient populations to ensure their effectiveness in different clinical settings [167]. Qian Yu et al. developed an automatic hepatic venous pressure gradient (HVPG) quantitative estimation model based on patients' CT images, which achieved non-invasive grading of hepatic venous pressure gradient in patients with cirrhosis and portal pressure gradient in patients with liver cirrhosis and portal hypertension. Its AUC exceeds 0.80, which is better than other non-invasive tools, providing an effective non-invasive HVPG primary prevention method for patients who cannot undergo transjugular HVPG measurements. However, the study had a certain degree of patient selection bias, and follow-up data were not collected for the patients in the study. In the future, non-portal hypertensive cirrhosis patients need to be included to update the model [168]. The application of deep learning in cirrhosis prognosis assessment has demonstrated its powerful capabilities in image processing and feature extraction, providing clinicians with more accurate and efficient diagnostic tools.

With the continuous advancement of technology and the accumulation of clinical data, artificial intelligence is expected to play a more important role in the prognostic assessment of cirrhosis. Future research requires larger sample sizes and well-defined model development, as well as continuous optimization and validation of existing technologies, to ensure the clinical application of artificial intelligence technology and further promote the application of artificial intelligence in the field of liver disease treatment to provide patients with more accurate diagnosis and treatment. Details of these studies are presented in Table 5 Furthermore, a number of open-source datasets and models relevant to liver disease research are currently available online, as detailed in Table 6 providing essential support for ongoing studies.

Future research directions in the prognostic assessment of liver cirrhosis

Cirrhosis refers to the terminal phase of chronic liver damage, with its pathological progression influenced by a multitude of factors including primary diseases, patient lifestyle, and genetic predispositions. These factors strongly complicate the accurate assessment of prognosis in patients with cirrhosis. Although generalized indicators such as the Child–Pugh score and MELD score are commonly used to evaluate the prognosis of these patients, they mainly reflect risks common to the broader patient population rather than specific risks pertaining to individual patients [36, 169–171]. Moreover, current biomarkers fall short in precisely forecasting complications or acute deteriorations. As cirrhosis progresses, the liver progressively loses functionality, leading to serious complications in the decompensated stage, such as portal

Table 5 US imaging techniques in patients with liver disease

First author, references	Image source	Statistical methods	Application scenario
Hetland et al. [150]	UC/ CT	ROC analysis	Diagnosis of decompensated cirrhosis
Bhanji et al. [152]	CT	Cox regression model	Prediction of HE
Kang et al. [153]	CT	Cox regression model	Prediction of death in patients with compensated and early decompensated cirrhosis
Engelmann et al. [154]	CT	Cox regression	Prediction of the occurrence of cirrhosis-related complications and mortality
Kim et al. [156]	CT	Logistic regression	NAFLD fibrosis risk assessment
Gidener et al. [159]	MRE	Cox regression analysis	Prediction of progression of CLD to cirrhosis
Gidener et al. [160]	MRE	Cox regression analysis	Prediction of progression to compensated and decompensated cirrhosis in NAFLD
Park et al. [161]	MRE	ROC analysis	NAFLD liver fibrosis recognition
Loomba et al. [162]	MRE	ROC analysis	NAFLD liver fibrosis recognition
Noureddin et al. [163]	MRI	Logistic regression	NAFLD liver fibrosis recognition
Yu et al. [90]	MRI	Inverse probability weighting and propensity score matching analysis	Diagnosis of cirrhosis and HCC
Wang et al. [165]	CT	Deep CNN model	Muscle division
Liu et al. [167]	CT MRI	Deep CNN model	Recognition of portal hypertension
Yu et al. [168]	CT	3D FCN Model	HVPG classification
Yasaka et al. [166]	MRI	DCNN model	Liver fibrosis staging

UC ulcerative colitis, *CT* computed tomography, *ROC* receiver operating characteristic, *HE* hepatic encephalopathy, *NAFLD*, non-alcoholic fatty liver disease, *MRE* magnetic resonance elastography, *CLD* chronic liver disease, *MRI* magnetic resonance imaging, *HCC* hepatocellular carcinoma, *CNN* convolutional neural network, *3D FCN* 3-dimensional fully convolutional network, *HVPG* hepatic venous pressure gradient, *DCNN* deep convolutional neural network

Table 6 List of open-source datasets and open-source models

Dataset name	Type	Brief introduction	Dataset address
Liver Tumor Segmentation (LiTS) challenge	Open-source dataset	This report presents the LiTS Benchmark. In collaboration with seven hospitals and research institutions, 75 liver and LiTS algorithms were trained on 131 CT volumes, and then tested on 70 unknown test images. The results showed that no single algorithm was the best for all tasks. LiTS remains an active research benchmark and resource, providing data and online evaluations	https://competitions.codalab.org/competitions/17094
Indian Liver Patient Dataset (ILPD)	Open-source dataset	A hybrid extreme gradient boosting model was used to predict liver disease for early detection and risk reduction. The dataset included 583 Indian patients, and the results showed that the new model is more accurate than traditional methods. This study demonstrates the potential of machine learning in healthcare, especially in disease predict	https://www.kaggle.com/datasets/uciml/indian-liver-patient-records
TCGA Liver Hepatocellular Carcinoma (LIHC) study	Open-source dataset	Hepatocellular carcinoma biological datasets, including genomics, transcriptomics, proteomics, and clinical data, with experimental strategies including methylation arrays, genotyping arrays, and tissue microarrays	https://portal.gdc.cancer.gov/projects/TCGA-LIHC
Gene Expression Omnibus (GEO)	Open-source dataset	GEO is a public gene expression database storing a large amount of high-throughput gene expression data and other forms of microarray data designed to provide scientists worldwide with easily searchable and downloadable experiments and datasets to support biomedical research	https://www.ncbi.nlm.nih.gov/geo/
The Cancer Genome Atlas (TCGA)	Open-source dataset	TCGA is a large cancer genomics research program designed to advance the understanding of cancer biology by providing genome sequencing, transcriptome sequencing, epigenetic data, and proteomics data for a variety of cancer samples	https://portal.gdc.cancer.gov/
Radiomics for Liver Disease Analysis	Open-source model	This is an open-source Python package for extracting radiomic features from medical imaging. Through this package, we aim to establish a reference standard for radiomic analysis and provide a tested and maintained open-source platform for simple and reproducible extraction of radiomic features. It is applicable to the image analysis of liver cirrhosis	https://github.com/AIM-Harvard/pyradiomics
Liver Disease Prediction Machine Learning	Open-source model	This is a Liver Disease Machine Learning Classification Capstone Project in fulfillment of the Udacity Azure ML Nanodegree. In this project, you will learn to deploy a machine learning model from scratch	https://github.com/chollette/Liver-Disease-Classification-Azure-ML-Capstone-Project
Liver Disease Prediction	Open-source model	A liver disease prediction using SVM classifier, Logistic regression and Random Forest. The aim was to compare which of the classifiers give a better result in terms of the accuracy, recall, f1-score and precision	https://github.com/DPsalmist/Liver-Disease-Prediction

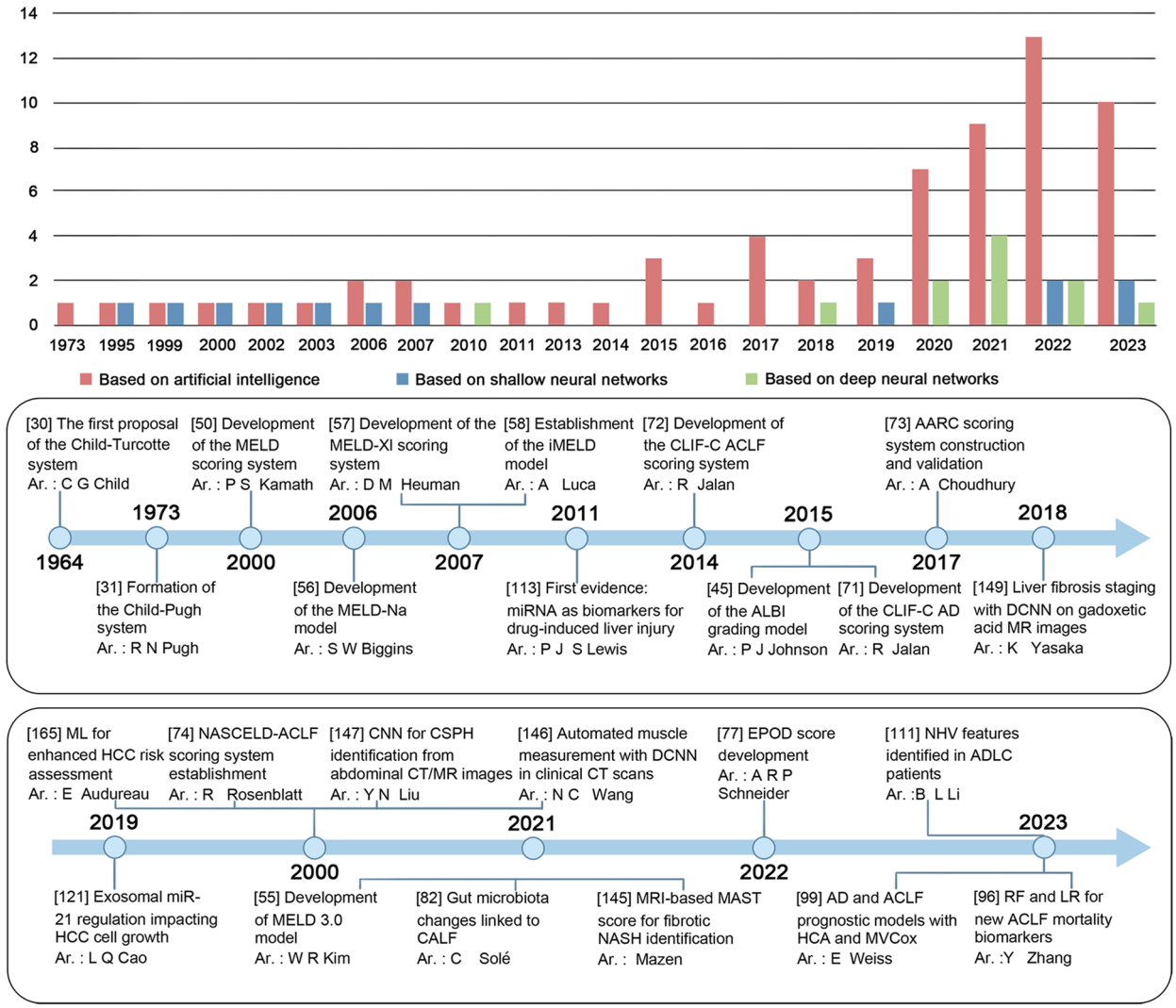

Fig. 3 Trends in liver cirrhosis prognostic assessment research: a graphical representation. **a** presents statistical analysis of annual publication volume related to AI application in liver cirrhosis prognostic assessment. It illustrates yearly literature output for all AI algorithms, including shallow and deep neural networks. The evolution of AI literature, particularly neural network algorithms, in liver cirrhosis prognostic assessment is described. **b** provides statistics and descriptions of significant milestone articles. It includes a historical overview of prognostic tools, advanced technology applications in immunobiochemistry and microbiology, miRNA, and the discovery history of new markers, highlighting evolutionary changes in cirrhosis prognostic assessment tools

hypertension, variceal bleeding, and HCC, all severely afflicting multiple organ systems. These conditions add to patient distress and economic burden and may lead to irreversible acute or chronic liver failure, driving the high mortality rate associated with liver cirrhosis [172–174].

For some individuals who survive decompensated cirrhosis, the complexity and severity of the disease require continuous medical interventions, which profoundly impact their quality of life and mental health. However, liver fibrosis and early stages of cirrhosis are reversible conditions. Timely and accurate assessment of the prognosis for patients with cirrhosis and appropriate adjustments of therapeutic strategies are vital to improving patient outcomes and reducing mortality rates [175, 176]. Consequently, the exploration of new methodologies and the development of innovative tools for prognostic assessment in cirrhosis are critical areas of focus for future liver disease research.

With the evolution of medical technologies, the research into the prognostic assessment of liver cirrhosis is advancing progressively, transitioning from traditional clinical scoring systems to innovative biomarkers derived from high-throughput technologies in immunology, microbiology, and miRNAs. Consult Fig. 3 for

additional details. Additionally, the integration of sophisticated imaging techniques and AI for analysis is improving the precision of these prognostic assessments. These cutting-edge technologies and methods not only increase the accuracy of cirrhosis prognosis but also enhance clinicians' understanding of disease progression, with the ultimate goal of improving patient outcomes. While the deployment of these innovative assessment tools promises to revolutionize traditional evaluation methods, it also presents a series of challenges, especially in the context of applying AI to the prognostic evaluation of cirrhosis.

From routine clinical and laboratory data research to multi-omics studies

Cirrhosis, as a chronic and progressive liver disease, is characterized by the insidious nature of early-stage symptoms and the complexity of the involvement of multiple comorbidities in later stages. Prognosis primarily depends on clinical observations, imaging tests, laboratory evaluations, and specific assessment tools, which encompass a diverse range of data sources and types. Clinicians are tasked with synthesizing a vast amount of data to make informed diagnostic and therapeutic decisions, facing the challenges of data heterogeneity and its dynamic nature [177–179]. Electronic health records (EHRs) provide crucial support for the effective integration and management of such data. However, traditional statistical analyses are inadequate in elucidating the intricate interrelations and interactions among numerous variables and lack the capacity to handle high-dimensional data, rendering them incapable for the analysis of cirrhosis patient data. Furthermore, laboratory and clinical data, confined to a single biological level or clinical manifestation, fall short of providing comprehensive insights into the molecular mechanisms of cirrhosis, restricting the accuracy and comprehensiveness of prognostic assessments. This presents a clear imperative for multidimensional biological research in cirrhosis.

The advancements of molecular biology research and the application of high-throughput technologies, such as mass spectrometry, next-generation sequencing, and gene chip technology, have provided access to data obtained across various biological dimensions, including genomics, transcriptomics, proteomics, and metabolomics. These tools offer new insights into understanding the complex interactions and regulatory interrelations among different biomolecules within organisms, unveiling the pathophysiological mechanisms of cirrhosis and providing a solid research foundation for comprehensively assessing the prognosis of liver cirrhosis [180–182].

Nevertheless, multi-omics data also face significant, inherent challenges due to their diversity, high dimensionality, large scale, and complexity. The complexity of processing multi-omics data far exceeds that of standard laboratory and clinical data, presenting stringent demands and challenges for data processing and analytical capacities [183, 184].

AI algorithms, especially machine learning algorithms, excel at handling nonlinear relationships and complex patterns, enabling them to adeptly capture intricate patterns and correlations whin data effectively. These algorithms are characterized by adaptability and flexibility, which allow them to automatically adjust and optimize based on the specific features of the data and the complexity of the problem [185, 186]. Consequently, they are highly efficient in processing large-scale and high-dimensional data. Thus, in the era of big data and advanced analytics, the integration of AI into the medical field, particularly for the prognostic assessment of liver cirrhosis, represents an inevitable development trend.

Mining of potential biomarkers for cirrhosis

Meanwhile, the application of advanced technologies and the development of multi-omics research provide powerful tools and platforms for mining potential biomarkers of liver cirrhosis. The analysis of cirrhosis-related data using AI technology helps to deepen the exploration of its pathophysiological mechanisms and lays the research foundation for the prognostic assessment of cirrhosis. For example, various machine learning and deep learning algorithms provide assistance in identifying microbial markers and US imaging picture features associated with cirrhosis. Furthermore, genes are essential in determining an individual's hereditary characteristics, including susceptibility to disease, physical characteristics, and even certain behavioral tendencies. Thus, genetic variants may affect key processes in the liver such as metabolism, immunity, and fibrosis. By analyzing the genome sequences of patients with cirrhosis, it is possible to identify genetic variants associated with the progression of cirrhosis [187, 188]. Transcriptomics and proteomics studies can analyze alternations of gene expression and protein modification status in tissues or blood of cirrhotic patients, respectively, which may further reflect the pathological changes in liver function [189]. However, according to our research, there are still relatively few relevant applications of AI in the exploration of cirrhosis-related biomarkers, and most studies have ignored the multi-omics data of cirrhosis. The application of AI has the potential to provide more accurate and reliable biomarkers for the diagnosis, treatment, and prognostic assessment of liver cirrhosis. In the future, researchers should further explore and validate the sensitivity and specificity of these biomarkers for prognostic assessment of cirrhosis. The accuracy of prognostic assessment of

cirrhosis is expected to be further improved by combining new biomarkers and predictive models.

Prediction of mortality in cirrhosis

The prognosis and mortality prediction in patients with cirrhosis are crucial for determining optimal timing of liver transplantation and other interventions. Traditional scoring systems like the Child–Pugh and MELD have their predictive limitation due to the inclusion of subjective metrics, which may not accurately reflect the prognosis of individual patients, posing constraints in clinical applications. AI, however, has demonstrated great potential for enhancing mortality prediction in cirrhotic patients [190–193].

For instance, in 2003, Banerjee et al. utilized an artificial neural network model to predict the one-year mortality rate of patients with cirrhosis, achieving an internal validation accuracy of 91%, with sensitivity and specificity rates of 90% and 92%, respectively. This model significantly outperformed the predictive capabilities of traditional logistic regression models and the Child–Pugh score [194]. Similarly, Cucchetti's team constructed an artificial neural network model based on data from 251 consecutive cirrhosis patients, which surpassed the performance of the MELD score in accurately predicting patients' risk of death within the next three months. This model provided essential guidance for better decision-making of the prioritization of liver transplantation candidates, effectively reducing the mortality rate of patients in the waiting list [195]. In another innovative application, Suzanne et al. employed the Random Forest machine learning algorithm to identify 13 macrogenomic features in NAFLD that serve as stronger predictors of death compared to the MELD model. The application of AI provided robust technical support for the analysis of complex macrogenomic data, extracting significant macrogenome-derived features by analyzing their complex relationships with hepatic decompensation. This method offers a new approach for predicting mortality risk in NAFLD-associated cirrhosis [196].

These groundbreaking results demonstrate the powerful ability of AI to mine the depth of clinical data and improve prediction accuracy. However, it is worth noting that most current AI-driven mortality prediction models still rely mainly on routine clinical data, such as laboratory test results and clinical manifestations, while ignoring multi-omics data [197, 198]. Omics data, including genomics, transcriptomics, proteomics, and metabolomics, can provide more comprehensive and in-depth biological information and reveal the molecular mechanisms of disease onset and development. For example, Suzanne R et al. used a random forest algorithm to screen 13 key features from metagenomic data of patients with non-alcoholic fatty liver disease (NAFLD) [196]. These features outperformed the MELD model as predictors of death, demonstrating the enormous potential of omics data in the prognostic assessment of cirrhosis. Exploring the establishment of a prognostic model for cirrhosis mortality based on omics data will be a crucial step toward improving prediction accuracy and achieving personalized medicine. It is expected to reveal the complex pathophysiological process of liver cirrhosis from a broader perspective, and to establish a more comprehensive and refined prognostic evaluation system by integrating multi-omics data [165, 197–199]. Although the application of omics data has shown great potential, it also faces several limitations and challenges. For example, technical and procedural differences between different laboratories make it difficult to directly integrate data, which affects the consistency and reliability of the analysis. The high dimension and complexity of omics data analysis makes the process extremely time-consuming, requiring the development of more efficient data preprocessing, dimensionality reduction and pattern recognition techniques. At the same time, privacy and ethical considerations are difficult issues that cannot be ignored. How to protect patient privacy while using this data in a legal and compliant manner has become a pressing issue that needs to be addressed. At the same time, most of the current mortality prediction models are based on small sample size, single-center studies, and the generalizability of the models has yet to be verified by further multicenter, large-scale studies [165, 199].

Prediction of complications related to cirrhosis

The management of cirrhosis, particularly at its terminal stages, is complicated with a variety of aggressive complications that can potentially lead to sudden mortality in patients.

Predicting mortality is indeed a crucial aspect of understanding patient survival and prognosis in the context of cirrhosis. The ability to predict the risk of complications provides insights into the specific health risks and the likely trajectory of disease progression, which is vital for early detection and intervention. This proactive approach aims to reduce the incidence and severity of complications, thereby improving the quality of life for patients and potentially decreasing mortality rates. However, cirrhosis and its associated complications present unique challenges for prediction. Each complication has distinct characteristics, and accurately assessing the risk associated with each is essential for effective diagnosis, treatment, and management of cirrhosis patients. Machine learning analytics, including support vector machines, decision trees, and random forests, are particularly valuable in identifying and learning patterns of correlation

between patient characteristics and the occurrence of complications from large and complex datasets. By doing so, they enable the prediction of potential complications that a patient with cirrhosis might experience, offering a significant advantage in the management of the disease. For instance, Singal developed a prediction model for HCC development in cirrhotic patients using regression analysis and machine learning algorithms. This model demonstrated that machine learning algorithms surpassed traditional regression models in predicting HCC development, enhancing the accuracy of risk stratification in cirrhotic patients and enabling the identification of those at high risk for HCC [200]. Similarly, the Audureau's team constructed an HCC predictive model based on clinical information from 836 patients with HCV-associated cirrhosis, using Fine-Gray regression as a baseline and integrating randomized survival forests with a single decision tree (DT) and competing risk of survival (RSF). This approach accurately predicted the risk of HCC based on patients' virologic status, enhancing the assessment of HCC risk in cirrhotic patients by revealing complex interactions between cancer predictors and providing guidance for developing more cost-effective customized surveillance programs [184]. Moreover, deep learning algorithms, which are based on artificial neural networks, have demonstrated significant capabilities in processing complex data and extracting advanced features. Deep neural network models have also contributed significantly to the predictive assessment of cirrhosis complications [201]. Fukuda et al. utilized a three-layer feed-forward neural network with a back-propagation algorithm to develop a neural network analysis system for the objective assessment of liver parenchymal echo patterns in patients with cirrhosis, calculating a coarse score (CS), which proved to be a useful predictor of the progression of HCC [202]. Additionally, the Lee's team constructed a deep learning model based on CT images and clinical information of 419 patients with B-virus compensated cirrhosis. The results demonstrated that the spleen volume, obtained using deep learning-based CT analysis combined with the platelet ratio, is useful for detecting high-risk varices and assessing the risk of variceal bleeding in patients with cirrhosis. These studies underscore the effectiveness of deep learning techniques in evaluating the risk of developing cirrhosis complications and in the intelligent stratification of patients [203]. A significant concentration of AI research in cirrhosis complications has been on the emergence of HCC and esophageal varices, with a specific focus on the associated bleeding risks [204–209]. Yet, there is a notable scarcity of studies addressing other complications such as ascites, HE, portal hypertension, liver failure, and portal vein thrombosis. Considering that each complication can cause varying degrees of irreversible damage to the patient, it is crucial for future research to address the risk of a broader spectrum of cirrhosis-related complications [168, 210–214].

Additionally, while complex machine learning models and deep learning neural networks have shown formidable capability in processing and analyzing complex data, their "black box" nature can obscure the interpretability, impacting the fairness and safety of the model output. Efforts to develop machine learning models that are interpretable, along with techniques and tools for explaining and interpreting model decisions, are pivotal in AI research. This focus on transparency is crucial for building trust in the use of AI for prognostic assessments in cirrhosis, ensuring that the advancements in AI contribute effectively and ethically to patient care.

Dynamic, multimodal prognostic model construction based on deep learning techniques

In conclusion, the comprehensive application of AI in the prognostic assessment of liver cirrhosis currently faces limitations due to the reliance on unimodal data. While unimodal data can provide insights into specific aspects, it does not fully capture the patient's overall condition and may restrict the accuracy and reliability of predictive models. In contrast, multimodal data offer a more comprehensive and precise representation, enhancing the assessment and prediction of the conditions in cirrhotic patients. Clinical data, laboratory results, and histologic data from cirrhosis patients provide a robust foundation for constructing multimodal models. Additionally, the complexity of the disease necessitates a robust understanding of the pathophysiological mechanisms and pathogenesis of cirrhosis, further advocating for the development of multimodal data processing models as an inevitable trend in AI applications for cirrhosis prognosis [216, 217]. The specific construction and data integration for these models are central to future research efforts. Deep learning, an advanced form of machine learning, leverages deeper neural network structures and more complex algorithms to perform intricate learning tasks and has become increasingly significant in the prognostic assessment of liver cirrhosis. However, studies utilizing deep learning techniques are relatively sparse, mostly based on shallow neural networks, indicating that the application of deep neural networks requires more profound development and implementation. Moreover, the heterogeneity and dynamic nature of diseases require the capacities of real-time condition monitoring. Technologies such as sensors and wearable devices provide continuous streams of data, enabling continuous monitoring of physiological parameters and patient activities. This data flow offers a research foundation for real-time

tracking of condition changes, producing extensive time-series data. Current literature reveals that most AI-based prediction models in the prognostic assessment of liver cirrhosis predominantly handle static data. Thus, utilizing dynamic data to construct real-time early warning assessment models represents another vital direction for future research, promising to transform the landscape of cirrhosis management and patient care [218, 219].

We anticipate that through joint efforts in multidisciplinary collaborative research and the integration and analysis of data from various domains, significant progress will be made in understanding the pathophysiological mechanisms of cirrhosis. Meanwhile, the development and implementation of multimodal models have the potential to make contributions. Such advancements are expected to culminate in the creation of a more accurate real-time early warning system for cirrhosis prognosis assessment. The overarching aim of these efforts is to effectively tackle the intractable live disease and enhance the precision of diagnostic and prognostic tools, ultimately improving patient outcomes and saving more lives.

Abbreviations

MELD	Model for end-stage liver disease
AI	Artificial intelligence
CLD	Chronic liver disease
GBD	Global burden of disease
NAFLD	Non-alcoholic fatty liver disease
ALD	Autoimmune liver disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HE	Hepatic encephalopathy
HCC	Hepatocellular carcinoma
CLIF-ACLF	Chronic liver failure acute-on-chronic liver failure
CLIF-C AD	Chronic liver failure consortium acute decompensation
EPOD	Early prediction of decompensation
ALBI	Albumin-bilirubin
Clif-C-ACLF	Chronic liver failure consortium acute-on-chronic liver failure
AARC	American association for respiratory care
NACSELD	North American consortium for the study of end-stage liver disease
ROC	Receiver operating characteristic
miRNA	MicroRNA
US	Ultrasound
INR	International normalized ratio
TIPS	Transjugular intrahepatic portosystemic shunt
SBP	Spontaneous bacterial peritonitis
BA	Bacterial infection
AUC	Area under the curve
MELD-Na	MELD with serum sodium
iMELD	Integrated MELD
OPTN	Organ procurement and transplantation network
CLIF-C OF	Chronic liver failure consortium organ failure
CysC	Cystatin C
uNAG	Urinary N-acetyl-β-D-glucosaminidase
t-Cort	Total cortisol
eAlb	Effective albumin concentration
uNGAL	Urinary neutrophil gelatinase-associated lipocalin
AKI	Acute kidney injury
L-FABP	Liver-type fatty acid binding protein
PSP	Presepsin
HVPG	Hepatic venous pressure gradient
SIBO	Small intestinal bacterial overgrowth
MDR	Multi-drug resistant
mNGS	Macro-genomic second-generation sequencing
MHE	Minimal hepatic encephalopathy
NASH	Non-alcoholic steatohepatitis
qPCR	Quantitative polymerase chain reaction
RND	Research and development
CT	Computed tomography
MRI	Magnetic resonance imaging
MRE	Magnetic resonance elastography
LSM	Liver stiffness measurement
DCNN	Deep convolutional neural network
CNN	Convolutional neural network
3D FCN	3D full convolution network
EHR	Electronic health record
CS	Coarse score
AT	Antithrombin
ELISA	Enzyme-linked immunosorbent assay
NHV	Non-hepatotropic virus
LiTS	Liver tumor segmentation
ILPD	Indian liver patient dataset
LIHC	Liver hepatocellular carcinoma
GEO	Gene expression omnibus
TCGA	The cancer genome atlas

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Author contributions
Y.P.Z.: Data Curation, Investigation, Writing—original draft. D.R.H.: Data Curation, Investigation, Writing—original draft. L.Z.: Data Curation, Investigation, Writing—original draft. C.Y.L.: Investigation, Methodology, Visualization. X.R.T.: Investigation, Methodology, Visualization. Z.F.M.: Investigation, Methodology, Visualization. Q.J.T.: Investigation, Methodology, Visualization. W.H.L.: Investigation, Methodology, Visualization. X.W.X.: Investigation, Methodology, Visualization. Q.Z.: Conceptualization, Funding acquisition, Project administration, Supervision, Writing—review & editing. J.W.S.: Conceptualization, Funding acquisition, Project administration, Supervision, Writing—review & editing. J.Y.P.: Conceptualization, Funding acquisition, Project administration, Supervision, Writing—review & editing.

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