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Treatment and prognostic assessment of liver cirrhosis and its complications, volume II

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Treatment and prognostic assessment of liver cirrhosis and its complications, volume II

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Editorial: Treatment and prognostic assessment of liver cirrhosis and its complications, volume II

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Editorial on the Research Topic
Treatment and prognostic assessment of liver cirrhosis and its complications, volume II

From an initial discussion with the in-house editors of Frontiers on November 23, 2023, a Research Topic entitled "*Treatment and prognostic assessment of liver cirrhosis and its complications, volume II*" was launched in Frontiers in Medicine on December 12, 2023. We received a large number of submissions until the deadline on August 4, 2024. Overall, a total of 21 papers involving 157 authors were published after internal editorial assessment, external peer review, and editorial decision processes. Interestingly, at the time of writing this editorial on March 27, 2025, they have been viewed or downloaded over 10 thousand times. Herein, their contents have been briefly summarized in the following sections.

Symptoms in liver cirrhosis

Philips from the Rajagiri Hospital, India, comprehensively reviewed several common symptoms, including malaise, fatigue, lethargy, appetite disorders, restrictive diet, malnutrition, non-cholestatic pruritus, muscle cramps, sleep disorders, mental health disorders, gastrointestinal symptoms, sexual dysfunction, pain, peripheral neurological symptoms, hair loss, and skin changes, in patients with liver cirrhosis, and summarized their management. Xie et al. from the Hebei Clinical Research Center for Digestive Diseases, China, performed a meta-analysis of 16 observational studies and demonstrated that the overall estimated prevalence of frailty was 27% in cirrhosis patients and that its occurrence was positively associated with patients who were male, older, had a lower BMI, or had worse liver function.

Pathogenesis of liver fibrosis

There are three papers regarding the pathogenesis of liver fibrosis. Hu et al. from the Shengjing Hospital of China Medical University, China, reviewed the role of Chitinase-3-like protein 1 in the pathogenesis and diagnosis of liver fibrosis. Shamsan et al. from the Qinghai University, China, comprehensively reviewed the role of the PI3k/AKT signaling pathway in attenuating liver fibrosis. Guo et al. from the Shandong University, China, performed a Mendelian randomization study to confirm the causal effects of cigarette smoking on liver fibrosis and cirrhosis.

Assessment of liver cancer

There are three papers regarding the assessment of risk factors and prognostic factors for liver cancer. Dong et al. from the General Hospital of Northern Theater Command, China, retrospectively analyzed the association of ABO blood groups and rhesus factor with primary liver cancer in liver cirrhosis. The researchers did not find any significant association between them in patients with cirrhosis. Qiao et al. from the Beijing You'an Hospital of Capital Medical University, China, developed a nomogram by combining gamma-glutamyl transpeptidase-to-platelet ratio, age, and hemoglobin to predict the overall survival of patients with compensated cirrhosis and hepatocellular carcinoma who were treated with local ablation. They demonstrated good predictive performance of this nomogram in such patients. Luo et al. from the Shulan (Hangzhou) Hospital Affiliated to Zhejiang Shuren University Shulan International Medical College, China, evaluated the role of γ-glutamyl transferase to serum albumin ratio in assessing the survival of patients with hepatocellular carcinoma who underwent liver transplantation. They demonstrated that the γ-glutamyl transferase to serum albumin ratio $\geq$2.04 was independently associated with recurrence-free and overall survival.

Assessment of portal hypertension

There are five papers regarding the assessment of portal hypertension. Shanka et al. from the I.M. Sechenov First Moscow State Medical University, Russia, systematically reviewed the evidence regarding non-invasive methods for diagnosis of portal hypertension in liver cirrhosis secondary to non-alcoholic fatty liver diseases or metabolic dysfunction-associated steatotic liver diseases. They suggested that the measurement of liver and spleen stiffness offered good diagnostic evaluation of clinically significant and severe portal hypertension. Mao et al. from the First Affiliated Hospital of Anhui Medical University, China, explored the diagnostic performance of esophageal varices' diameters, which were measured using a virtual ruler under endoscopy, to assess portal pressure gradient, which in turn was measured using interventional radiology. Cao et al. from the same study group also performed a multicenter study to evaluate the diagnostic performance of esophageal varices diameter, which was also measured using a virtual ruler under endoscopy, to predict the risk of early rebleeding within 6 weeks after endoscopic variceal ligation. The novelty of the two studies is in the use of a virtual ruler-based measurement of esophageal varices. The researchers found that an esophageal varices diameter of >1.1 cm and $\geq$1.4 cm with a virtual ruler were related to a significantly increased portal pressure gradient level of 20 mmHg and early rebleeding in cirrhosis, respectively. Li et al. from the Women and Children's Hospital of Chongqing Medical University, China, developed and internally validated a clinical-radiomics nomogram by combining prothrombin time, sarcopenia, and radiomics score to predict the occurrence of upper gastrointestinal bleeding in liver cirrhosis. Notably, the radiomics score was established by extracting 11 different features on CT images. Ye et al. from the West China Hospital of Sichuan University, China, evaluated the association of metabolites with severe portal hypertension indicated by a hepatic venous pressure gradient of >16 mmHg in Tibetan patients with liver cirrhosis. Notably, by using metabolomics, the researchers identified pisumionoside and N-decanoylglycine as promising biomarkers for severe portal hypertension.

Assessment of prognosis from other aspects

Gülcicegi et al. from the University Hospital Cologne, Germany, evaluated the role of dynamic changes in spleen stiffness after starting acute decompensation treatment in hospitalized cirrhotic patients. They found a gradual decrease in spleen stiffness after effective treatment. Que et al. from the Daping Hospital of the Army Medical University, China, developed a novel prognostic model by combining age, ascites, albumin, prothrombin time, total bilirubin, and sodium in patients with viral hepatitis-related cirrhosis who were treated by transjugular intrahepatic portosystemic shunt (TIPS). They found that the novel post-TIPS prognostic model had good predictive performance. Wang S. et al. from the Peking University People's Hospital, China, retrospectively evaluated the risk factors of the first liver-related readmission within 30–90 days after the index hospitalization. They found that hepatic encephalopathy, ascites, and spontaneous bacterial peritonitis caused a higher risk of prehospitalization.

Treatment of liver cirrhosis-related complications

There are three case reports, one retrospective study, and one meta-analysis regarding the treatment of liver cirrhosis-related complications. Liu et al. from the Beijing Xiaotangshan Hospital, China, reported a case of hepatic myelopathy that was successfully treated by liver transplantation and comprehensive rehabilitation training. Sun et al. from the Gansu Provincial Hospital, China, reported a case of gastric variceal bleeding that was successfully treated by TIPS via the mesenteric venous pathway. Wang R. et al. from the General Hospital of Northern Theater Command, China, reported a case of liver cirrhosis with acute symptomatic portal vein system thrombosis that developed after endoscopic variceal therapy and was successfully treated by immediate anticoagulation. Tie et al. from the Xijing Hospital of Digestive Diseases of the Air Force Medical

University, China, evaluated the efficacy of variceal embolization for primary prophylaxis of variceal bleeding in cirrhotic patients who were not suitable candidates for non-selective beta blockers or endoscopic treatments. They demonstrated that variceal embolization achieved a high rate of technical success and low rates of recurrence and severe complications. Yang et al. from the People's Hospital of Guangxi Zhuang Autonomous Region and Guangxi Academy of Medical Sciences, China, conducted a meta-analysis and showed the benefits of probiotics for hepatic encephalopathy reversal, liver function, quality of life improvement, and gut dysbiosis regulation in patients with cirrhosis.

We hope that the findings from the papers published in this Research Topic can have a substantial impact on real-world clinical practice. We also expect to initiate Volume III of the Research Topic in the near future and receive more interesting and valuable papers.

Author contributions

WZ: Writing – review & editing, Writing – original draft, Investigation. YT: Writing – original draft, Writing – review & editing, Investigation. HW: Writing – original draft, Writing – review & editing, Investigation. AM: Writing – review & editing, Writing – original draft, Investigation. TT: Investigation, Writing – review & editing, Writing – original draft. XQ: Supervision, Conceptualization, Writing – review & editing, Investigation, Writing – original draft, Project administration.

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Conflict of interest

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The role of PI3k/AKT signaling pathway in attenuating liver fibrosis: a comprehensive review

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Excessive accumulation of extracellular matrix (ECM) components within the liver leads to a pathological condition known as liver fibrosis. Alcohol abuse, non-alcoholic fatty liver disease (NAFLD), autoimmune issues, and viral hepatitis cause chronic liver injury. Exploring potential therapeutic targets and understanding the molecular mechanisms involved in liver fibrosis are essential for the development of effective interventions. The goal of this comprehensive review is to explain how the PI3K/AKT signaling pathway contributes to the reduction of liver fibrosis. The potential of this pathway as a therapeutic target is investigated through a summary of results from *in vivo* and *in vitro* studies. Studies focusing on PI3K/AKT activation have shown a significant decrease in fibrosis markers and a significant improvement in liver function. The review emphasizes how this pathway may prevent ECM synthesis and hepatic stellate cell (HSC) activation, ultimately reducing the fibrotic response. The specific mechanisms and downstream effectors of the PI3K/AKT pathway in liver fibrosis constitute a rapidly developing field of study. In conclusion, the PI3K/AKT signaling pathway plays a significant role in attenuating liver fibrosis. Its complex role in regulating HSC activation and ECM production, demonstrated both *in vitro* and *in vivo*, underscores its potential as a effective therapeutic approach for managing liver fibrosis and slowing disease progression. A comprehensive review of this field provides valuable insights into its future developments and implications for clinical applications.

KEYWORDS

liver fibrosis, attenuating liver fibrosis, PI3K/Akt pathway, hepatic stellate cells, extracellular matrix

1 Introduction

1.1 Overview of liver fibrosis

Liver fibrosis is a modern condition characterized by the excessive accumulation of ECM proteins in the liver due to chronic injuries (1). These proteins include collagen and alpha-smooth muscle actin (α-SMA), which are highly responsive to liver injuries and can lead to more serious conditions such as cirrhosis and hepatocellular carcinomas. This condition is a global problem, affecting thousands of people. Various factors, including viral infections,

alcohol abuse, autoimmune issues, and NAFLD contribute to the development of liver fibrosis. Understanding the underlying mechanisms and exploring therapeutic techniques is essential for managing this health condition (2, 3).

Mechanistically, liver fibrosis initiates with continual liver injury, and activated HSCs play a crucial role by transforming into myofibroblast-like cells, contributing to ECM production (4). Signaling pathways, particularly the transforming growth factor-beta (TGF-β) pathway, play a pivotal role in regulating ECM synthesis and inhibiting breakdown (5). Chronic inflammation, driven by immune cells releasing pro-inflammatory cytokines, creates a microenvironment that sustains fibrotic processes. The crosstalk among hepatocytes, immune cells, and HSCs influences fibrosis development (6).

On the therapeutic front, the latest approaches focus on inhibiting fibrogenesis. Anti-fibrotic markers targeting HSC activation and ECM production show promising results in both preclinical and clinical research. Immunomodulatory processes and the Inhibition of the TGF-β signaling pathway are explored as potential strategies. Addressing metabolic factors, such as obesity and insulin resistance, is gaining attention, and precision medication tailors interventions to individual variations in fibrotic responses (7, 8).

Understanding the mechanisms of liver fibrosis is critical for developing effective therapies. Recent development in anti-fibrotic strategies offers hope for improved patient outcomes and offer avenues for further research and development.

1.2 Overview of PI3K/AKT

The PI3K/AKT intracellular signaling pathway plays a significant role in various cellular processes, including survival, proliferation, metabolism and cell growth. Liver fibrosis is involved the regulation of numerous physiological and pathological conditions (9). The pathway consists of several key components, including protein kinase B (AKT) and phosphatidylinositol 3-kinase (PI3K), which is also referred to as a serine/threonine kinase (10).

PI3K is a lipid kinase that phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 serves as a second messenger and recruits AKT to the plasma membrane, where it is activated by phosphorylation. Activated AKT then phosphorylates downstream targets, leading to the activation of various signaling pathways (11).

Multiple mechanisms regulate the PI3K/AKT pathway to maintain cellular homeostasis. Various extracellular stimuli, such as cytokines, hormones, and growth factors, can be activated. These stimuli bind to their specific receptors and initiate a series of intracellular activity. Furthermore, the tensin homolog PTEN inhibits the AKT activation pathway (12).

In the liver fibrosis context, the PI3K/AKT signaling pathway has been demonstrated to play a significant role in both the attenuation and development of liver fibrotic processes. Examples of chronic liver injury include alcohol abuse, viral hepatitis and NAFLD, all of which can cause hepatic fibrosis. The excessive accumulation of ECM proteins, including collagen, is characterized by the disruption of liver architecture and impairment of liver function in liver fibrosis (13).

2 Components and regulation of PI3K/AKT signaling pathway

The PI3K/AKT signaling pathway is strictly regulated to prevent aberrant activation and maintain cellular homeostasis. Multiple mechanisms control the activity of this pathway, including:

1 Activation of RTKs: Receptor tyrosine kinases (RTKs) are transmembrane proteins that cross the cell membrane and bind to specific ligands, such as hormones and growth factors. RTKs undergo autophosphorylation in response to ligand binding, leading to the activation of downstream signaling cascades (14). Ligand binding to RTKs is the main mechanism through which the PI3K/AKT pathway is triggered. The interaction between ligands and receptors induces conformational changes in the receptor, causing autophosphorylation and subsequent activation of downstream signaling (15).
2 Negative regulation by PTEN: PTEN, a lipid phosphatase that antagonizes the activity of PI3K by dephosphorylating PIP3, thereby inhibiting downstream signaling through the PI3K/AKT pathway (16). By acting as a negative regulator of the PI3K/AKT pathway, PTEN regulates liver fibrosis. Liver fibrosis can develop as a result of hyperactivation of the pathway caused by mutations in the PTEN gene or loss of PTEN function (17).
3 Activation of PI3Ks: RTKs activate PI3Ks, which constitute a family of lipid kinases. Phosphorylinositol 3,4,5-trisphosphate (PIP3) is produced by phosphorylating phosphatidylinositol 4,5-bisphosphate (PIP2) through PI3Ks (18). PIP3 attracts proteins with pleckstrin homology (PH) domains to the cell membrane and acts as a second messenger (1). Upon RTKs activation, PIP2 is phosphorylated to generate PIP3, and PI3Ks are recruited to the cell membrane. The recruitment and activation of downstream signaling molecules depend on this phase (19).
4 Activation of Akt: Akt is activated by phosphorylation at two critical sites, Ser473 and Thr308. PDK1 is responsible for mediating phosphorylation at Thr308, whereas mTORC2 is the catalyst for phosphorylation at Ser473. These phosphorylation events are essential for subsequent downstream signaling and Akt activation (20). Akt inhibits GSK3β, leading to the stabilization of β-catenin and resulting in the downregulation of ECM synthesis (21).
5 Negative feedback loops: To prevent excessive activation, the PI3K/AKT pathway is subject to negative feedback regulation. Several proteins, such as the suppressor of cytokine signaling (SOCS) family and insulin receptor substrate (IRS) proteins, can inhibit upstream signaling components, thereby attenuating pathway activity (22).

SOCS proteins regulate cytokine signaling by inhibiting JAK/STAT pathways, while IRS proteins mediate insulin and growth factor receptor signaling. The interplay between SOCS and IRS involves SOCS impacting cytokine pathways, indirectly influencing IRS function and insulin signaling. This dynamic regulation ensures cellular homeostasis in response to various extracellular signals (23).

SOCS and IRS proteins work synergistically in negative feedback loops to modulate the PI3K/AKT pathway (18).

SOCS inhibits upstream signaling components such as Janus kinase (JAK) leading to IRS proteins undergo inhibitory phosphorylation, collectively leading to the attenuation of PI3K/AKT signaling by inhibiting JAK activity, which is upstream of PI3K/AKT pathway. This interference blocks the transmission of signals from cytokine receptors to PI3K/AKT, thus dampening the pathway (24).

In summary, SOCS and IRS act as important modulators in preventing excessive activation of the PI3K/AKT pathway. SOCS proteins provide negative feedback in response to cytokines, while IRS proteins, particularly in the context of insulin signaling, are regulated to ensure proper cellular responses and maintain homeostasis.

A brief outline of the components and regulation of the PI3K/AKT signaling pathway mechanism is depicted in Figure 1.

3 Function of PI3K/AKT signaling pathway in normal physiology

The PI3K/AKT pathway is strictly controlled in normal physiology to ensure appropriate cellular reactions to various stimuli (25).

One of the main functions of the AKT pathway in normal physiology is to regulate cell development. Activation of this pathway stimulating protein synthesis and inhibiting apoptosis, promoting cell growth. AKT, the downstream effector of PI3K, phosphorylates and inactivates pro- apoptotic proteins, such as Bad and caspase-9, thereby promoting cell survival (26).

AKT activation moves glucose transporters, such as glucose transporter 4 (GLUT4), to the cell membrane, promoting glucose absorption and utilization. Increased absorption and consumption of glucose as a result gives cells the energy they require to function. Furthermore, AKT activation promotes the production of glycogen and prevents its breakdown, allowing the body to maintain glucose homeostasis (27).

The PI3K/AKT pathway also plays a role in control of cell proliferation and protein synthesis. Activation of AKT stimulates protein synthesis by activating the mTORC1, a pivotal regulator of protein translation (28).

Activation of mTORC1 leads to the phosphorylation of downstream effectors, including S6K and 4E-BP1, promoting cell growth and protein synthesis (29). Furthermore, by blocking the action of cyclin-dependent kinase inhibitors like p21 and p27, AKT activation advances the cell cycle and permits cell division (30). Angiogenesis is controlled by the AKT/PI3K pathway. Activation of AKT stimulates the synthesis of vascular endothelial growth factor (VEGF) (31). Angiogenesis is largely aided by VEGF, whose production is triggered by AKT activation. This process encourages migration and proliferation of endothelial cell, which results in the creation of new blood vessels (32). Tissue repair and growth, as well as the transport of nutrients and oxygen to tissues, rely on the creation of new blood vessels (15, 25). In Figure 2, the function of PI3K/AKT in normal physiology is outlined.

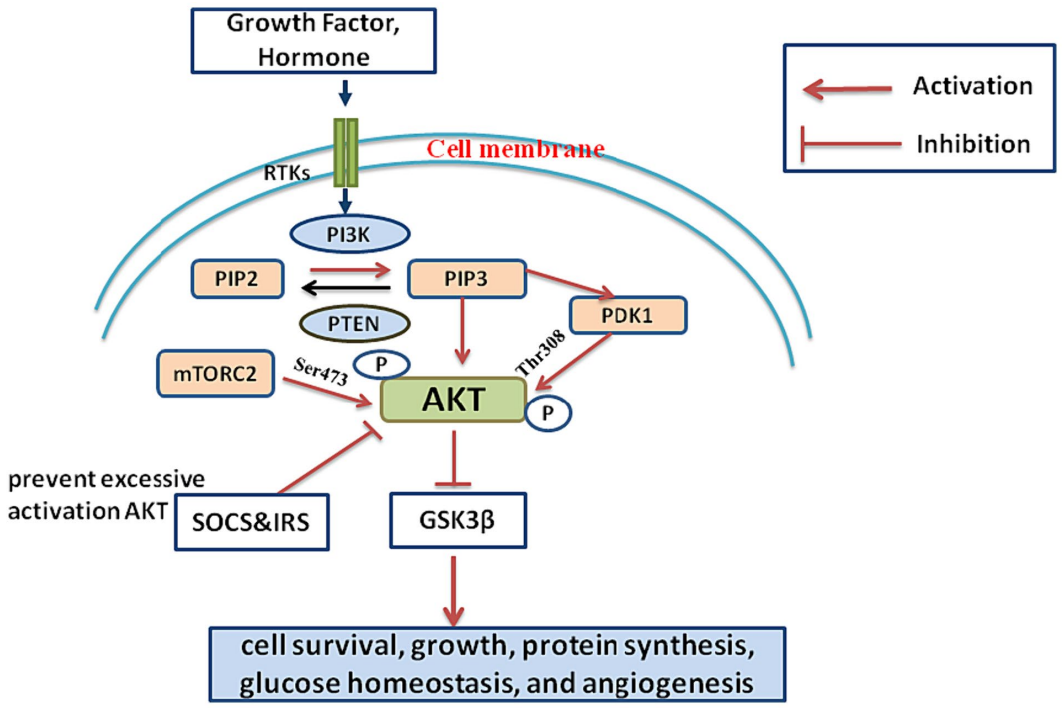

FIGURE 1
Growth factors and hormones activate receptor tyrosine kinases (RTKs) on the cell membrane. RTK activation initiates the activation of PI3K. PI3K converts PIP2 into PIP3. PIP3 recruits AKT to the cell membrane. AKT is phosphorylated and activated by PDK1 and mTORC2. AKT phosphorylates various downstream effectors. GSK3β, Inhibition of GSK3β stabilizes β-catenin, leading to downregulation of ECM synthesis. This cascade regulates cell survival, growth, protein synthesis, glucose homeostasis, and angiogenesis. SOCS and IRS are key regulators in preventing excessive activation of the PI3K/AKT pathway.

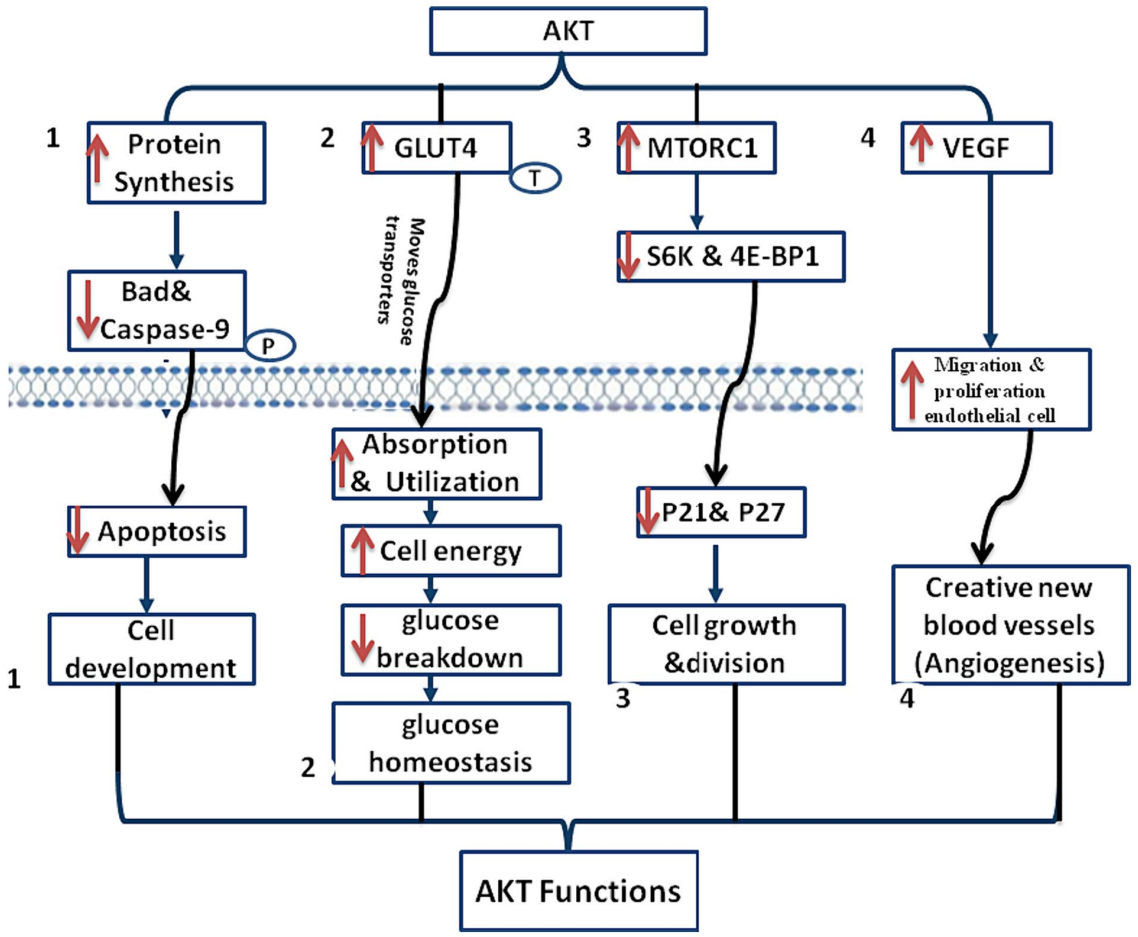

FIGURE 2
This diagram shows AKT/PI3K function, (1) Cell development regulation: AKT pathway regulates cell development by stimulating protein synthesis and inhibiting apoptosis through the phosphorylation of pro-apoptotic proteins like Bad and caspase-9, promotes cell development, (2) glucose homeostasis: AKT activation facilitates glucose homeostasis by enhancing glucose utilization and absorption, ensuring ample energy for cellular functions, and preventing glycogen breakdown, (3) cell proliferation and protein synthesis: AKT promotes cell proliferation and protein synthesis by activating mTORC1, which phosphorylates key effectors (S6K and 4E-BP1), promoting cell growth. AKT activation advances the cell cycle by blocking inhibitors (p21 and p27), permitting cell division, and (4) angiogenesis control: AKT/PI3K pathway controls angiogenesis by stimulating VEGF synthesis, promoting endothelial cell migration and proliferation for the formation of new blood vessels. Essential for tissue repair, growth, and efficient transport of nutrients and oxygen to tissues.

In general, the PI3K/AKT signaling pathway plays a pivotal role in overseeing of the body's normal physiological functions. It governs entire biological processes, ensuring appropriate cellular responses to various stimuli. Dysregulation of this pathway is associated with the development of liver fibrosis. Understanding the functional nature of the PI3K/AKT signaling pathway is essential to elucidating its importance and role in alleviating liver fibrosis.

4 PI3K/AKT signaling pathway in liver fibrosis

Studies have shown that the development and attenuation of liver fibrosis are significantly influenced by the PI3K/AKT pathway, with varying degree of activation observed at different stages of liver disease. The pathway is activated in the early stages of fibrosis, promoting hepatocyte survival and regeneration. However, as fibrosis worsens, the process is blocked, leading to the overproduction of ECM proteins and the activation of HSCs (33).

There are many ways to attenuate liver fibrosis through the PI3K/AKT signaling pathway. Studies have shown that activation of the pathway can reduce HSC proliferation and activation, decrease ECM production, and promote hepatocyte survival and regeneration. Furthermore, the pathway has the ability to control oxidative stress and inflammatory reactions, which are two major factors in liver fibrosis (8).

The role of the PI3K/AKT signaling pathway in reducing and inducing liver fibrosis has been investigated in several clinical and experimental studies (8). Targeting the pathway for the treatment of liver fibrosis has the potential to yield therapeutic advantages, as shown by these studies. However, further research is needed to fully understand the underlying mechanisms and identify potential therapeutic targets within the pathway (32).

In liver fibrosis, the PI3K/AKT signaling pathway plays a significant role in regulating cellular processes (34). Although AKT pathway activation can mitigate fibrotic processes, dysregulation of the pathway contributes to the onset and progression of fibrosis. Understanding of the pathways via which liver fibrosis is regulated could be helpful in developing new treatment approaches for this debilitating illness (35).

4.1 PI3K/AKT signaling pathway in development of liver fibrosis

The PI3K/AKT signaling pathway plays a crucial role in various biological functions. Understanding its involvement in liver fibrosis has garnered more attention in recent years. Liver fibrosis is characterized by the excessive accumulation of ECM, a progressive condition that impairs liver function and affects liver architecture (36).

Several cellular function are regulated by the PI3K/AKT signaling pathway, which is activated by cytokines, various growth factors and other extracellular signals binding to cell surface receptors, initiating a series of intracellular events (14). The process begins with the activation of PI3K, which phosphorylates PIP2 to generate PIP3 (37, 38). Subsequently, AKT is recruited to the plasma membrane by PIP3, where it undergoes phosphorylation and activation by PDK1 and mTORC2 (39).

Studies have demonstrated that the PI3K/AKT signaling pathway enhances the activation and proliferation of HSCs, the primary cell type responsible for excessive ECM production in liver fibrosis (40). Increased cell survival, proliferation, and migration in HSCs, along with higher collagen and other ECM protein production, are all outcomes of PI3K/AKT pathway activation. This promotes the growth and worsening of liver fibrosis (41). A brief outline of liver fibrosis mechanism is shown in the Figure 3.

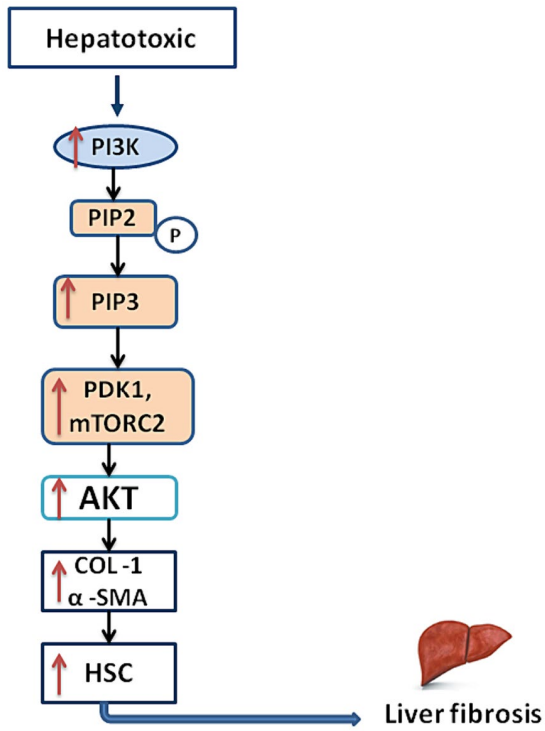

FIGURE 3
This diagram illustrates the mechanism of liver fibrosis, starting with the activation of PI3K, followed by the phosphorylation of PIP2 to generate PIP3, which activates PDK1 and mTORC2. Subsequently, AKT is activated at the plasma membrane by PDK1 and mTORC2. The PI3K/AKT signaling pathway exhibits a role in liver fibrosis, promoting the activation, proliferation, and excessive production of extracellular matrix (ECM) proteins in hepatic stellate cells (HSCs).

4.2 PI3K/AKT signaling pathway in attenuating liver fibrosis

The PI3K/AKT signaling pathway exhibits a dual function in liver fibrosis, playing roles in both development and attenuation. Regarding the attenuation of liver fibrosis, the pathway emerges as a critical player, offering potential therapeutic avenues for liver cirrhosis. Chronic liver injury triggers the progressive scarring process of liver fibrosis (42, 43).

The reduction of liver fibrosis has also been linked to the PI3K/AKT signaling pathway (44, 45). Numerous investigations have indicated that the activation of AKT decrease the synthesis of collagen, α-SMA, and activation of HSCs, ultimately contributing to fibrosis regression (46). AKT activation inhibits the expression of profibrogenic genes in HSCs, including TGF-β and α-SMA. Additionally, the activated AKT induces the expression of matrix metalloproteinases (MMPs), enzymes involved in ECM breakdown (47). The precise mechanisms by which the PI3K/AKT pathway reduces liver fibrosis are not fully understood. AKT activation leads to inhibition of nuclear factor kappa B (NF-κB), a transcription factor crucial in inflammation and fibrogenesis (48), This inhibition may be companied by a reducing in pro-inflammatory cytokines, such interleukin-6 (IL-6) and tumor necrosis factor- alpha (TNF-α) levels (49), While anti-inflammatory cytokines like interleukin-10 (IL-10) are increased. Suggesting that the activation of AKT improves the resolution of liver fibrosis and reduces the inflammatory response (50).

This inhibition could contribute to the attenuation of liver fibrosis, as collagen production and HSC activation are linked to NF-κB activation (51). Another potential mechanism is the regulation of the TGF-β signaling pathway by the PI3K/AKT pathway (52). AKT activation inhibits TGF-β signaling by phosphorylating and inactivating Smad proteins, downstream effectors of the TGF-β pathway (53).

The potential role of TGF-β signaling suppression in the anti-fibrotic actions of the PI3K/AKT pathway cannot be overlooked (54, 55). Furthermore, Liver fibrosis is significantly impacted by oxidative stress, characterized by an imbalance between the antioxidant defense system and the generation of reactive oxidative stress (ROS). Studies have shown that the PI3K/AKT signaling system regulates oxidative stress by controlling the production and activity of antioxidant enzyme (56). Activation of AKT leads to increased expression of antioxidant enzymes, such as Superoxide dismutase (SOD) and catalase, which scavenge ROS and protect against oxidative damage (57). The PI3K/AKT pathway attenuates liver fibrosis and promote liver regeneration by regulating ROS (58).

In Addition, apoptosis or programmed cell death, is essential in resolution of liver fibrosis. It has been demonstrated that the PI3K/

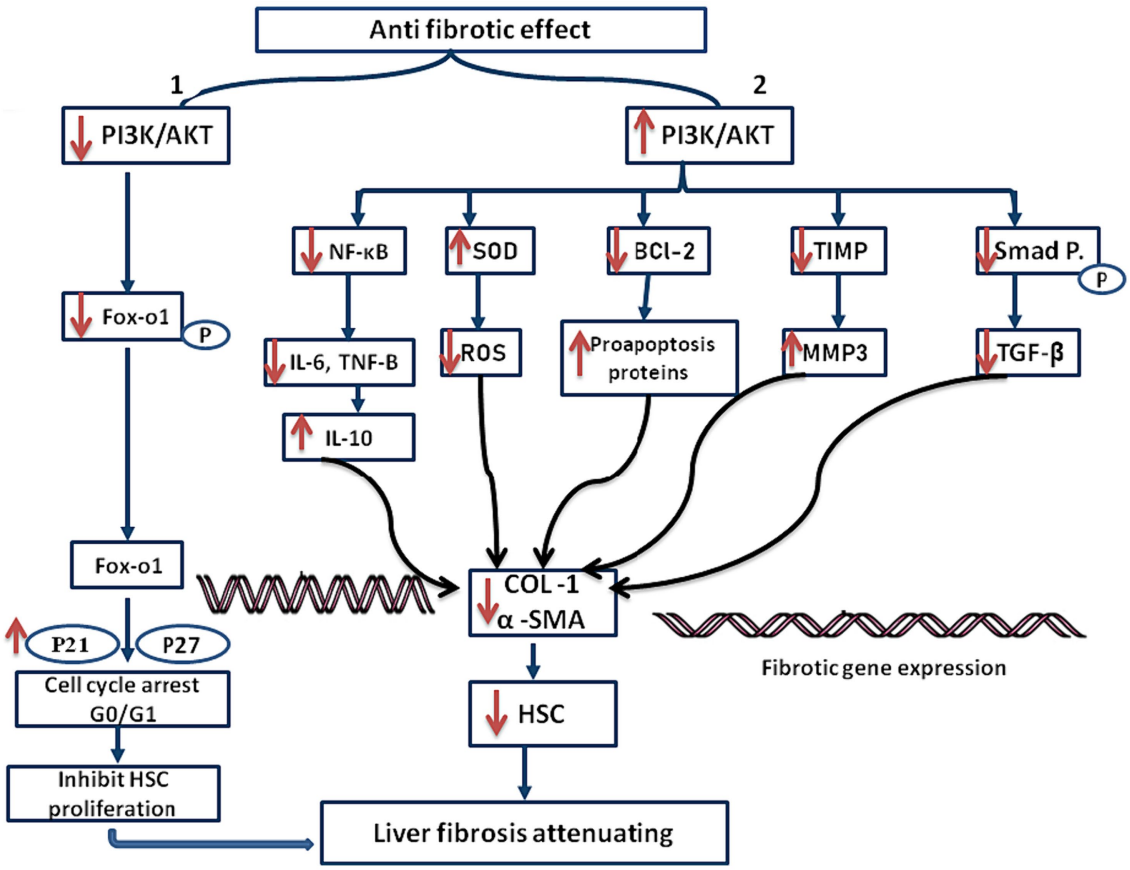

FIGURE 4
Mechanism of anti fibrotic effect in attenuating liver fibrosis. (1) Ant fibrotic effect decreases phosphorylation of Akt and FoxO1, which leads to FoxO1 nuclear translocation. This event leads to the upregulation of p21 and p27 protein expression, inducing G0/G1 phase arrest and subsequently inhibiting the proliferation of hepatic stellate cells (HSCs), (2) this diagram illustrates how the PI3K/AKT signaling pathway reduces liver fibrosis by inhibiting collagen, α-SMA, and HSC activation. The pathway's activation leads to the inhibition of profibrogenic gene expression, possibly through NF-κB inhibition via AKT activation. AKT also regulates the TGF-β signaling pathway, inhibiting downstream effects and contributing to anti-fibrotic actions. The suppression of TGF-β signaling is highlighted as a key aspect of the pathway's anti-fibrotic effects.

AKT signaling pathway causes active HSCs to undergo apoptosis, which facilitates the liver's removal of these cells. Pro-survival proteins, such as Bcl-2 are phosphorylated and rendered inactive during activation of AKT, while pro-apoptotic proteins are stimulated. This change in the ratio of pro-apoptotic to pro-survival proteins triggers the apoptotic cascade, ultimately eliminating activated HSCs and improving liver fibrosis (55, 59).

Besides, Liver fibrosis is characterized by excessive accumulation and inadequate the degradation of ECM proteins. The regulation of ECM remodeling has been linked to the PI3K/AKT signaling system, which modulates the activity of MMPs and tissue inhibitors of TIMPs. Studies have shown that AKT activation enhances MMP production and activity, potentially leading to ECM protein degradation (60).

The PI3K/AKT pathway's role in liver fibrosis extends beyond promotion, with studies indicating its anti-fibrotic effects. Activating the pathway, either pharmacologically using specific agonists or through genetic manipulation, has demonstrated promising results in animal models of chronic liver injury (61). These interventions lead to the inhibition of HSC activation, reduced collagen deposition, and improved liver function (62). The coordination between the pro-fibrotic and anti-fibrotic effects of the PI3K/AKT pathway determines its overall impact on liver fibrosis (61).

In contrast, activation of the PI3K/AKT pathway promotes the activation of HSCs, the main cell type responsible for the production of ECM proteins in liver fibrosis (63). Activated HSCs undergo a process called transdifferentiation, acquiring a myofibroblast-like phenotype characterized by increased proliferation, migration, and production of collagen and other ECM proteins (64). The PI3K/AKT pathway has been shown to promote HSC activation and fibrogenesis through various mechanisms, including the up regulation of TGF-β signaling and the inhibition of apoptosis (62).

While most studies suggest that activating the AKT pathway contributes to the alleviation of liver cirrhosis, contrasting research has shown that inhibiting the AKT pathway also leads to the attenuation of liver cirrhosis. This occurs through the downregulation of Akt/FoxO1 phosphorylation, resulting in the nuclear translocation of Forkhead box protein O1 (FoxO1). Consequently, there is an upregulation of P21 and P27 expression, ultimately causing cell cycle arrest in the G1 phase and effectively inhibits HSC proliferation (28, 65, 66). These divergent findings highlight the current lack of clarity regarding this mechanism, underscoring the need for further elucidation.

A brief outline of the mechanism involved in attenuating liver fibrosis is shown in Figure 4.

TABLE 1 Overview of traditional Chinese medicine targeting the PI3K/AKT pathway to alleviate liver fibrosis.

Compounds	*In vitro* activity	*In vivo* activity	Activity in human	References
Xiaoyaosan (XYS)	Not assessed	Yes - rats	Not assessed	(74)
Sini San (SNS)	Yes - HepGz cells	Yes - mice	Not assessed	(75)
Ginsenoside Rh2 (GRHs)	Yes - HSC-TG	Yes - mice	Not assessed	(30)
Corn oligopeptides (COPs)	Not assessed	Yes - mice	Not assessed	(76)
Dahuang Zhechong Pills (DHZCP)	Not assessed	Yes - rats	Not assessed	(77)
Bilberry fruits extract (BEs)	Yes - mouse hepatic AML-12cells	Yes - mice	Not assessed	(78)
Propolis	Not assessed	Yes - male BalB/C mice	Not ASSESSED	(79)
Corydalis saxicola Bunting Total Alkaloids (CSBTA)	Yes - HepG2	Yes - mice	Not assessed	(80)
Ginsenoside Rk3	Not assessed	Yes - C57BL/6 mice	Not assessed	(14)
Arctigenin (ATG)	Yes - HSCs	Yes	Not assessed	(7)
Astragaloside IV (AS-IV)	Not assessed	Yes - rats	Not assessed	(81)
Dihydroartemisinin (DHA)	Yes - HSCs	Yes - rats	Not assessed	(82)
Germacrone (GM)	Yes - HSC- LX-2	Yes - rats	Not assessed	(69)
Gypenosides	Yes - HSCs	Yes - rats	Not assessed	(83)
Songyou Yin (SYY)	Yes - HSCs	Yes - nude mice	Not assessed	(84)
Lycium barbarum polysaccharides (LBPs)	Not assessed	Yes - female rats	Not assessed	(85)
Puerarin	Not assessed	Yes - C57BL/6 J mice	Not assessed	(86)
Total alkaloids of Corydalis saxicola Bunting (TACS)	Not assessed	Yes - rats	Not assessed	(87)
Semen Brassicae extract	Not assessed	Yes - Male Sprague–Dawley rats	Not assessed	(34)
Sennoside A (SA)	Yes - HSC-T6 cells	Yes - mouse	Not assessed	(88)
Yu Jin Pulvis (YJP)	Not assessed	Yes - mouse	Not assessed	(89)
Yu Gan Long (YGL)	Not assessed	Yes - rat	Not assessed	(9)
Didymin	Yes - HSCs	Yes - rat	Not assessed	(90)
Silibinin	Yes - LX-2	Not assessed	Not assessed	(91)
Caffeic acid phenethyl ester (CAPE)	Yes - HSC-T6	Yes - male Sprague–Dawley rats	Not assessed	(92)
Ginsenoside Rg2	Yes - HSC-T6	Yes - rat	Not assessed	(38)
Glycyrrhizin (GL)	Yes - splenic CD4(+)T cells	Yes - concanavalin A (ConA)-induced mouse	Not assessed	(93)
Thymoquinone	Yes - T-HSC/Cl-6	Yes - mice	Not assessed	(94)
Berberine	Yes - HSC	Yes - classical mouse	Not assessed	(95)
Tanshinol	Not assessed	Yes - male Sprague–Dawley (SD) rats.	Not assessed	(96)
Curcumin	Yes - HSC	Yes - rats	Not assessed	(97)

5 Interplay of PI3K/AKT and Nrf2 signaling pathway in mitigating liver fibrosis

In the context of liver fibrosis, the PI3K/AKT signaling pathway plays a pivotal role in fibrotic progression, and its interplay with the nuclear factor arythroid 2- related factor 2 (Nrf2) pathway introduces an additional layer of complexity to the regulatory mechanisms underlying fibrosis progression. Activation of the PI3K/AKT pathway not only promotes cell survival and inhibits apoptosis but also amplifies Nrf2-mediated antioxidant responses (67). Furthermore, pharmacological modulation of PI3K/AKT signaling augments Nrf2 activity and alleviates liver fibrosis in experimental models (68). A deeper understanding of the complex crosstalk between these signaling pathways hold promise for the development of targeted therapeutic strategies for effective liver fibrosis management.

6 Investigating PI3K/AKT signaling pathway: clinical insights and experimental evidence

Research studies have shown that the PI3K/AKT signaling pathway plays a vital role in reducing or attenuating liver fibrosis both *in vivo* and *in vitro*. It has been demonstrated that triggering this pathway enhances liver function, inhibit the activation of HSC, and

TABLE 2 Survey of herbal extracts compounds targeting the PI3K/AKT pathway for liver fibrosis alleviation.

Compounds	*In vitro* activity	*In vivo* activity	Activity in human	References
Carthami flos extract (CFE)	Not assessed	Yes - mice	Not assessed	(98)
Esculetin	Not assessed	Yes - Wistar rats	Not assessed	(99)
25-OCH3-PPD, a ginsenoside isolated from *Panax ginseng*	Not assessed	Yes - mice	Not assessed	(100)
Cichorium pumilum Jacq extract (CGEA)	Yes - RAW264.7 cells.	Yes - rats	Not assessed	(70)
Tanshinone IIA (TIIA)	Yes - HSC-LX2	Yes - rats	Not assessed	(101)
Luteolin	Yes - HSCs and HSC-T6 Cell	Yes - mice Sprague–Dawley rats	Not assessed	(102)
Naringin	Not assessed	Yes - rat	Not assessed	(103)
Aronia melanocarpa polysaccharide (AMP)	Not assessed	Yes - TAA-induced liver fibrosis mice	Not assessed	(53)
Lycopene	Not assessed	Yes - rats	Not assessed	(104)

decrease the markers of liver fibrosis. These results demonstrate the therapeutic potential of treating fibrosis by targeting the PI3K/AKT signaling system.

These investigations provide valuable insights into the potential therapeutic possibilities of intervening with this pathway. Researchers have evaluated the impact of PI3K/AKT modulation on liver fibrosis and explored its underlying mechanisms through the scrutiny of both *in vivo* and *in vitro* trials.

In a research conducted by Cai et al. (69), the consequences of PI3K/AKT signaling pathway activation on liver fibrosis were explored using a rat model. Their study revealed that inducing this pathway with a particular agonist substantially decreased liver fibrosis indicators. These results indicate the potential effectiveness of PI3K/AKT activation in mitigating liver fibrosis both *in vivo* and *in vitro*.

Likewise, in an *in vitro* investigation by Han et al. (70), the focus was on the role of the PI3K/AKT signaling pathway in HSC activation, a pivotal step in liver fibrosis development. Their findings revealed that inhibiting the PI3K/AKT pathway using specific inhibitor suppressed HSC activation and decreased the production of fibrotic markers, including CTGF and TGF-β. These outcomes indicate that targeting the PI3K/AKT pathway can inhibit HSC activation and potentially hinder the progression of liver fibrosis.

In another clinical investigation by Baghaei and colleagues (71), the primary focus was on evaluating the therapeutic potential of PI3K/AKT pathway modulation in liver fibrosis patients. The research team conducted a randomized controlled trial where patients were subjected to PI3K/AKT activator treatment for a specific duration. Their observations showed a significant improvement in liver function tests, as well as a reduction in fibrosis markers, such as collagen type III N-terminal peptide and hyaluronic acid. These results suggest that activating the PI3K/AKT pathway may have clinical benefits in ameliorating liver fibrosis in human patients.

Moreover, a study conducted by Li and colleagues (72), explored the effects of PI3K/AKT pathway modulation in the context of liver fibrosis using a cell culture model. In this study, the researchers treated HSC with a PI3K/AKT activator. The result revealed observed a decrease in cell proliferation and collagen production. Additionally, they found that the activated PI3K/AKT pathway inhibited the expression of fibrotic genes, like tissue inhibitor of metalloproteinase-1 and alpha-1 type I collagen. These results provide compelling evidence that PI3K/AKT activation can directly influence fibrotic processes in liver cells.

In another *in vitro* study led by Xiu et al. (73), the researchers investigated the molecular mechanisms underlying the protective attributes of the PI3K/AKT pathway concerning liver fibrosis. Their finding unveiled that activating this pathway inhibited HSC activation and reduced the expression of fibrotic markers, such as CTGF and TGF-β. Furthermore, the researchers observed that PI3K/AKT activation suppressed the nuclear translocation of Smad3, a pivotal mediator in the TGF-β signaling pathway. These findings provide insights into the molecular mechanisms by which the PI3K/AKT pathway mitigates liver fibrosis.

Presented below, Tables 1–5 compile research studies that have investigated the alleviation of liver fibrosis via the PI3K/AKT pathway, including *in vitro* and *in vivo* investigations as well as clinical studies.

MicroRNAs (miRNAs) play a crucial role in attenuating liver fibrosis by targeting the PI3K/AKT pathway. Acting as post-transcriptional regulators, miRNAs modulate key components of the pathway, disrupting the signaling cascade that contributes to fibrogenesis. This regulation mitigates the activation of hepatic stellate cells and the excessive production of extracellular matrix proteins, offering potential therapeutic interventions. Notable studies exploring the role of miRNAs in liver fibrosis and the PI3K/AKT pathway include references (64). These findings highlight the promise of miRNA-based strategies for targeted and personalized therapies against liver fibrosis.

Below is Table 4, featuring two research studies that explored the mitigation of liver fibrosis by targeting the PI3K/AKT pathway using microRNA interventions (Table 5).

7 Conclusion

In conclusion, the PI3K/AKT pathway plays an important role in mitigating liver fibrosis. It acts through multifaceted mechanisms, involving promotion of ECM degradation, inhibition of HSC activation, anti-apoptotic effects, and anti-inflammatory in the liver.

Studies emphasize the therapeutic potential of targeting the PI3K/AKT pathway for liver fibrosis. *In vitro* and *In vivo* studies support its role in improving liver function, ameliorating fibrosis and inhibiting ECM production.

TABLE 3 Summary of chemical compounds targeting the PI3K/AKT pathway for liver fibrosis alleviation.

Compounds	*In vitro* activity	*In vivo* activity	Activity in human	References
Adiponectin-based agonist called JT003	Y - HEK293 cells, HepG2 cells, and LX2 cells	Yes - NASH mice	Not assessed	(105)
Aspirin, ticlopidine, and cilostazol	Not assessed	Yes - fisher 344 male rats	Not assessed	(106)
FTY720	Not assessed	Yes - male Sprague–Dawley rats	Not assessed	(107)
Hesperetin	Yes - HepG2 cells	Yes - rats	Not assessed	(33)
Maltol	Not assessed	Yes - mice	Not assessed	(108)
A6	Not assessed	Yes - mice	Not assessed	(109)
Ruangan granules (RGGs)	Not assessed	Yes - rat	Not assessed	(110)
Salvianolic acid A (SA-A)	Not assessed	Yes - rat	Not assessed	(111)
Salvianolic acid B (SAB)	Not assessed	Yes - male C57 mice	Not assessed	(66)
Simvastatin	Not assessed	Yes - male Wistar rats	Not assessed	(112)
Doxazosin	Yes - HCS-LX-2	Yes - mouse	Not assessed	(73)
Artesunate (ART)	HSC- LX-2	Not assessed	Not assessed	(113)
5-BDBD	Not assessed	Yes - C57BL/6 J mice	Not assessed	(114)
Nilotinib	Yes - human HCS	Yes - rat	Yes	(89)
Idazoxan	Yes - LX-2	Yes - rat	Not assessed	(67)
Celecoxib	Yes - human HSCs	Yes - rat	Not assessed	(115)
Tenofovir disoproxil fumarate (TDF)	Not assessed	Not assessed	Chronic hepatitis B	(116)
Octreotide	Yes - HSCs	Yes - rat	Not assessed	(117)
JD5037	Not assessed	Yes - rat	Yes - liver fibrosis patients	(118)
Imatinib mesylate (STI-571)	Not assessed	Yes - rat	Assessed	(119)
Pyrazinamide (PZA)	Not assessed	Yes - Sprague–Dawley (SD) rats	Not assessed	(120)
Metformin	Not assessed	Yes - rats	Not assessed	(121)
Metformin	Yes - Cell lines (PLCPRF5 cells)	Yes - NOG mice	Yes - hepatocellular carcinoma (HCC) patients after liver transplantation	(122)
Propranolol	Yes - LX-2	Yes - mouse	Not assessed	(123)
Rapamycin	Not assessed	Yes - rats	Not assessed	(124)
Sorafenib	Not assessed	Yes - rats	Not assessed	(125)
Rimonabant	Not assessed	Yes - rats	Not assessed	(126)
1,8-cineole	Not assessed	Yes - knockout mice	Not assessed	(127)
Actein	Not assessed	Yes - mice	Not assessed	(128)
S-adenosylmethionine (SAM)	Yes - human colon cancer cells	Yes - MAT1A-KO mice	Not assessed	(129)
Sirolimus	Not assessed	Yes - PCK rats	Not assessed	(56)
Vevorisertib	Yes - Hep3B, HepG2, HuH7, and PLC/PRF cell lines	Yes - rats	Not assessed	(130)
Quercetin	Not assessed	Yes - mice	Not assessed	(131)
Resveratrol (RSV)	Yes - HSC-T6 cells	Yes - rat	Not assessed	(132)
Dihydromyricetin (DHM)	Not assessed	Yes - mice	Not assessed	(133)
Hemistepsin A (HsA)	Yes - HSCs	Yes - male ICR mice	Not assessed	(134)
Asiatic acid (AA) isolated from *Centella asiatica*	Not assessed	Yes - Rat	Not assessed	(135)
Cytisine derivatives, including compound 5f	Human LX-Cell	Not assessed	Not assessed	(136)
Atractylenolide III (ATL III)	Not assessed	Yes - mice	Not assessed	(137)
Tormentic Acid (TA)	Not assessed	Yes - Rat	Not assessed	(138)

(Continued)

TABLE 3 (Continued)

Compounds	*In vitro* activity	*In vivo* activity	Activity in human	References
Taxifolin	Not assessed	Yes - mouse	Not assessed	(139)
Honokiol	Yes - AML-12 hepatocytes	Yes - mouse	Not assessed	(140)
Hovenianin A	Yes - HSCs	Not assessed	Not assessed	(141)
Epigallocatechin-3-gallate (EGCG)	Yes - human HSC-XL-2	Yes - bile duct-ligated (BDL) rats.	Not assessed	(142)
Isovitexin	Not assessed	Yes - mice	Not assessed	(143)
Alpha mangostin	Yes - HSC	Not assessed	Not assessed	(144)
Hesperitin derivative-11 (HD-11)	Yes - HSC-T6 cells	Yes - rats	Not assessed	(145)
Matrine derivative WM130	Yes - HSC-IL-2	Yes - rats	Not assessed	(146, 147)

TABLE 4 Summary of microRNAs targeting the PI3K/AKT pathway for attenuating liver fibrosis.

Compound	*In vitro* activation	*In vivo* activation	Human activity	References
miR-29b	Yes - LX-1 and HSC-T6 cells	Yes - mouse	Yes assessed	(64)
miR-101	Yes - HSC-LX-2	Yes - mouse	Not assessed	(148)

TABLE 5 Summary of biological compounds targeting the PI3K/AKT pathway for attenuating liver fibrosis.

Compound	*In vitro* activation	*In vivo* activation	Human activity	Reference
Erythropoietin (EPO)	Not assessed	Yes - rat	Not assessed	(149)

The pathway's beneficial effects are intricate and entail the modulation of several downstream signaling pathways, including GSK-3β, mTOR and FOXO3a, which impact apoptosis, cell proliferation, and metabolism.

The PI3K/AKT signaling pathway is a promising target for liver fibrosis therapy, with potential therapeutic candidates, including AKT and PI3K isoforms, as well as downstream effectors, showing encouraging prospects and preclinical results for future clinical use.

Author contributions

ES: Writing – original draft, Writing – review & editing. MA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. NK: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AQ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LC: Writing – original draft, Writing – review & editing. FH: Writing – original draft, Writing – review & editing.

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Conflict of 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.

Publisher's note

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Glossary

Protein kinase B	AKT
Phosphoinositide 3-kinases	PI3Ks
phosphatidylinositol 4,5-bisphosphate	PIP2
phosphatidylinositol 3,4,5-trisphosphate	PIP3
Extracellular matrix	ECM
Hepatic stellate cells	HSCs
phosphoinositide-dependent kinase 1	PDK1
Mammalian target of rapamycin complex 1	mTORC2
Matrix metalloproteinases	MMPs
Pleckstrin homology	PH
Phosphoinositide-dependent kinase 1	PDK1
Glucose Transporter 4	GLUT4
Vascular endothelial growth factor	VEGF
Reactive oxygen species	ROS
Superoxide dismutase	SOD
Ribosomal protein S6 kinase	S6K
Eukaryotic initiation factor 4E-binding protein 1	4E-BP1
Interleukin- 6	IL-6
Interleukin- 10	IL-10
Tumor necrosis factor-alpha	TNF-α
Non-alcohol fatty liver disease	NAFLD
alpha-smooth muscle actin	α-SMA
B-cell lymphoma 2	Bcl-2
Glycogen Synthase Kinase 3 Beta	GSK3β
Tissue Inhibitors of Metalloproteinases	TIMPs
Suppressor of cytokine signaling	SOCS
Insulin receptor substrate	IRS
Phosphatase and Tensin	PTEN

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Probiotics are beneficial for liver cirrhosis: a systematic review and meta-analysis of randomized control trials

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Introduction: Gut dysbiosis may play a pivotal role in the pathogenesis of cirrhosis and the severity of complications. Numerous studies have investigated the probiotics as treatments for cirrhosis. However, there is still a lack of definitive evidence confirming the beneficial effects of probiotics on cirrhosis.

Methods: Databases including PubMed, Embase, Web of Science, and the Cochrane Library were systematically searched for randomized controlled trials that compared the effects of probiotic intervention and control treatments, including placebo, no treatment, and active control, on cirrhosis, published from inception to February 2024. Outcomes included hepatic encephalopathy (HE) reversal, safety and tolerability of probiotics, liver function, quality of life, and other cirrhotic-related outcomes. A meta-analysis was conducted to synthesize evidence.

Results: Thirty studies were included. The quantitative synthesis results showed that compared with the control group, probiotics significantly reverse minimal hepatic encephalopathy (MHE) (risk ratio [RR] 1.54, 95% confidence interval [CI] 1.03 to 2.32) and improve HE (RR 1.94, 95% CI 1.24 to 3.06). Additionally, probiotics demonstrated higher safety and tolerability by causing a lower incidence of serious adverse events (RR 0.71, 95% CI 0.58 to 0.87). Probiotics could potentially improve liver function by reducing the Model for End-Stage Liver Disease (MELD) scores (standardized mean difference [SMD] -0.57, 95% CI -0.85 to −0.30), and displayed favorable changes in quality of life (SMD 0.51, 95% CI 0.27 to 0.75) and gut flora (SMD 1.67, 95% CI 1.28 to 2.06).

Conclusion: This systematic review and meta-analysis offers compelling evidence that probiotics are beneficial for cirrhosis by demonstrating reversal of HE, potential for liver function improvements, enhancements in quality of life, and regulation of gut dysbiosis. Furthermore, the apparent safety profile suggests that probiotics are a promising intervention for treating cirrhosis.

Clinical trial registration number: CRD42023478380.

KEYWORDS

probiotics, liver cirrhosis, hepatic encephalopathy, liver function, meta-analysis

1 Introduction

Liver cirrhosis is the end stage of chronic liver disease, commonly caused by viral hepatitis, nonalcoholic steatohepatitis, and alcohol (1). Cirrhosis is within the top 20 causes of disability-adjusted life years and years of life lost, accounting for 1.6 and 2.1% of the global burden (2). Being a major cause of morbidity and mortality among individuals with chronic liver disease worldwide, cirrhosis affects over 160 million people and results in more than 1.3 million deaths each year (3–5). As currently one of the top 10 leading causes of death globally, cirrhosis imposes a great health burden in many countries (6). The burden has escalated at the worldwide level since 1990, partly because of population growth and aging (5). Thus, it is meaningful to explore effective treatments for reversing cirrhosis and preventing severe liver function and even systemic damage.

It has been proven that the occurrence and progression of cirrhosis are directly or indirectly associated with local and systemic immune and inflammatory changes (7). The gut microbiota can contribute to systemic inflammation (8). Changes in the gut microbiota are related to immune homeostasis disturbances (9). Therefore, studies have indicated that gut dysbiosis may play a role in the pathogenesis of cirrhosis, contributing to the severity of complications such as hepatic encephalopathy (HE), hepatocellular carcinoma, and the progression of acute-on-chronic liver failure (10, 11). Recognizing the association between gut imbalance and liver cirrhosis, an increasing number of studies have focused on the use of probiotics among patients with cirrhosis.

Probiotics are presently defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (12). In the context of aging, evidence shows that probiotics are valuable modulators of age-related pathologies and morbidity (13). Emerging studies are exploring various probiotic supplements for the treatment of cirrhosis. Some studies have suggested the effectiveness of probiotic therapy in cirrhotic patients. For example, one study employed *Lactobacillus* to prevent cirrhosis, and the results indicated an improvement in dysbiosis (14). Another clinical trial demonstrated that *Bifidobacterium* can promote the transformation of macrophages and control the inflammatory response among cirrhotic patients (15). However, some other studies did not demonstrate a significant protective effect of probiotic supplementation on cirrhosis (16, 17). These conflicting results may be partially due to the small size of cohorts or the biased design of individual trials, which could be solved by a meta-analysis. Although there were meta-analyses exploring the effect of probiotics on cirrhosis, most of the studies focused on patients during the progressive period of minimal hepatic encephalopathy (MHE) or HE (18, 19). Early detection and timely treatment of cirrhosis are essential to improving the outcomes of cirrhotic patients. Moreover, there is a study (20) that did not exclusively focus on randomized controlled trials (RCTs) to conduct a comprehensive analysis, preventing it from reaching the pinnacle of the evidence pyramid. Clear evidence is urgently needed to determine whether probiotics have beneficial effects on cirrhosis during any progressive period.

Thus, this systematic review and meta-analysis were conducted based on RCTs to assess the comparative outcomes of cirrhosis, including HE reversal, liver function, gut microbial taxonomy, and mortality, between probiotic and control treatments using quantitative statistical methods. A definitive conclusion on the therapeutic effects of probiotics will be derived to provide evidence for the efficacy of probiotics among cirrhotic patients.

2 Materials and methods

This systematic review and meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (21).

2.1 Search strategy

PubMed, Embase, Web of Science, and the Cochrane Library were systematically searched for RCTs comparing the effects of probiotic intervention with control treatments in patients with cirrhosis, published in English from inception to February 2024. A search strategy was developed based on keywords, medical subject headings (MeSH) terms, and synonyms (Supplementary Table S1). In addition to the database searches, we meticulously reviewed the reference lists of reviews, original studies, and related systematic reviews to identify additional studies potentially eligible for inclusion that could have been overlooked in our initial search.

2.2 Selection criteria

To meet the inclusion criteria, studies had to: (1) be conducted among patients aged more than 18 years, with any type of liver cirrhosis irrespective of etiology, during any disease-progressive period; (2) be RCTs that compared any probiotic intervention at any dose for any duration in a treatment group against a control group receiving placebo, no treatment, or active control treatment, including lactulose (22), rifaximin (23), placebo, standard treatment, or no treatment; and (3) report clinical outcomes related to cirrhosis such as ammonia levels, adverse events after receiving probiotics, liver functions, and mortality. In the study conducting co-interventions of probiotics and prebiotics or medication, equal doses of prebiotics or medication had to be administered in the control groups to ensure exploring the effect of probiotic intervention alone.

The exclusion criteria were as follows: (1) animal experiments or *in vitro* studies; (2) reviews, meta-analysis, comment, letter, poster abstract, editorial, case report, and correction; (3) papers could not be downloaded from databases; (4) a lack of data information available for synthesis analysis.

2.3 Study selection and data extraction

The titles and abstracts identified through the database searches were exported to EndNote X9, and duplicates were removed. The review process was carried out according to the guidelines laid out in the QUOROM statement (24). Two investigators (XY and LL) independently reviewed the titles and abstracts of all identified studies that were eligible for inclusion. Then, a full-text review of the potential papers was conducted to determine the final included studies. Another reviewers (WS and XL) were available for the final determination of whether a publication should be included if there were discrepancies.

Data extraction of the included studies was done using a pre-designed standardized Excel form that included the following information: author, country, study period, target population, interventions of treatment or control group, sample size, treatment period, study duration, and main findings.

2.4 Quality assessment

The quality of individual trials was assessed using the Cochrane Risk of Bias instrument (25), evaluating seven key domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Two reviewers (XY and LL) independently worked on the quality assessment. If there were any disagreements between reviewers, another two reviewers (WS and XL) were found to arbitrate.

2.5 Assessment of heterogeneity and publication bias

Both the Chi^2 test and the Higgins I^2 test were applied to assess the heterogeneity of studies in meta-analysis. When the p-value of the Chi^2 test was less than 0.05 and I^2 exceeded 50%, a random-effects model was selected, while a fixed model would be chosen if the results showed a p-value more than 0.05 and I^2 below 50%. Sensitivity analysis would be conducted if the model was unstable. Publication bias was assessed by funnel plot analysis. Egger's test was used for continuous outcomes, while Peter's test was conducted among dichotomous outcomes. A p-value >0.05 means no evidence of publication bias; otherwise, there would be a publication bias.

2.6 Outcome measures

Two researchers (XY and LL) coded the outcome measurements related to the effect of probiotics on cirrhosis for each included study separately. If there existed discrepancies, the two coding results were compared and discussed with another two researchers (WS and XL). Outcomes were finally categorized into the following seven main aspects: HE reversal, safety and tolerability of probiotics, liver function measurements, quality of life, effect on gut flora, inflammatory cytokines changes, and mortality.

2.7 Statistical analysis

Risk ratio (RR) and corresponding 95% confidence interval (CI) were used to assess the differences between probiotics and control groups when outcomes were dichotomous, while standardized mean difference (SMD) and 95% CI were used to evaluate the differences for continuous outcomes. If the outcomes were measured at a different time point, the terminal follow-up visits were chosen to be analyzed. Additionally, we conducted subgroup analyses for different types of probiotics and different intervention durations. A fixed-effects or random-effects model was selected according to the deviance information criterion (DIC). All tests were two-sided, with a p-value of 0.05 set as the threshold for significance. Through R 4.3.1, a forest plot was built for each outcome in the R package meta,[1] and the result of the risk of bias was visualized by the R package robvis.[2]

3 Results

3.1 Literature selection

Database searching identified 4,635 records, and 18 records were identified from other sources. There were 2,871 titles and abstracts screening after duplicates were removed. Then, 2,729 irrelevant and ineligible records were excluded, and 142 articles were used to conduct a full-text screening. After further excluding 112 articles for various reasons, a total of 30 RCTs were finally included in the systematic review and meta-analysis (Figure 1).

3.2 Study characteristics

Among the 30 trials that compared the therapeutic effect of probiotic treatment with control treatment in liver cirrhosis, 17 compared probiotics with placebo (17, 26–41), 7 compared probiotics with lactulose (42–47) or fermentable fiber (48), 3 compared probiotics with standard treatment (49–51), and 2 compared probiotics with no treatment (52, 53). And the control treatments in the remaining trial were lactulose and rifaximin (54). These studies were from 14 countries and contained a total of 2,084 cirrhotic patients, including 1,049 in the probiotic group and 1,035 in the control group (Table 1). Different subtypes and dosages of probiotics were used in different trials (Supplementary Table S2). More comprehensive details of the included studies are presented in Supplementary Tables S2–S3.

3.3 Probiotics reverse HE associated with liver cirrhosis

Seventeen studies were conducted among cirrhotic patients with different stages of HE (26, 27, 37–40, 42, 44–48, 50–54). Parameters containing ammonia level and neuropsychometric or neurophysiological status were measured to evaluate the improvement of HE. Results demonstrated that probiotic intervention could reverse MHE (RR = 1.54; 95% CI, 1.03 to 2.32; $p < 0.05$) and improve HE (RR = 1.94; 95% CI, 1.24 to 3.06; $p < 0.01$) significantly (Figure 2). Based on the subgroup analysis of probiotic types, the results show that compared to other types of probiotics, the VSL#3 probiotic (containing *Streptococcus*, *Bifidobacterium*, and *Lactobacillus*) has a more significant improvement effect on HE (RR = 1.44; 95% CI, 1.00 to 2.07; $p < 0.05$; Figure S1). A notable reduction was detected in both venous (SMD = −0.36; 95% CI, −0.57 to −0.15; $p < 0.001$) and arterial ammonia levels (SMD = −0.22; 95% CI, −0.44 to −0.01; $p < 0.05$) within the probiotic group versus the control group (Figure 3). The

1 http://CRAN.R-project.org/package=meta

2 https://cran.r-project.org/package=robvis

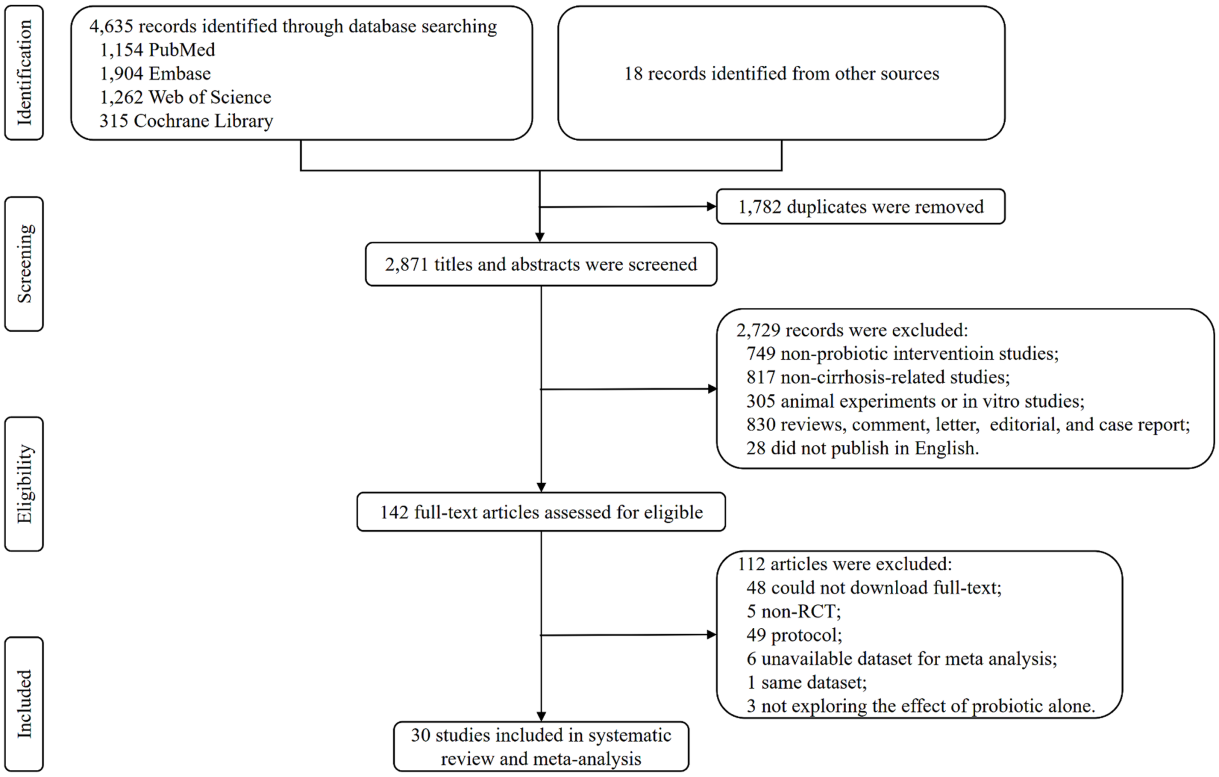

FIGURE 1
Flow chart of the study selection procedure.

results of the subgroup analysis of time of ammonia showed that, with the extension of follow-up time, the reduction level of ammonia was more significant at 3 months (SMD = −0.34; 95% CI, −0.56 to −0.11; $p < 0.01$; Figure S2). According to the neuropsychometric tests, significant higher digit symbol test (DST) scores were shown among cirrhotic patients with MHE in the probiotic group (SMD = 0.39; 95% CI, 0.01 to 0.78; $p < 0.05$; Figure 4A), while no significant change was detected in the number connection test (NCT) and figure connection test (FCT) (Figure 4B). A significant improvement in critical flicker frequency (CFF) was observed in the probiotic group based on neurophysiological test results (SMD = 0.69; 95% CI, 0.41 to 0.98; $p < 0.001$; Figure 5). Sensitivity analysis showed the overall effect size of venous ammonia would be impacted by removing a single effect size (Supplementary Figure S3).

3.4 Probiotics exhibit higher safety and tolerability

Compared with the control treatment including lactulose, rifaximin, placebo, and standard therapy, there was a significantly lower incidence of serious adverse events among patients receiving probiotic treatment (RR = 0.71; 95% CI, 0.58 to 0.87; $p < 0.001$; Figure 6). As the intervention time extended, patients with overt HE development (RR = 0.64; 95% CI, 0.48 to 0.85; $p < 0.01$; Supplementary Figure S4), hospitalization (RR = 0.58; 95% CI, 0.36 to 0.93; $p < 0.05$; Supplementary Figure S5), and infections (RR = 0.44; 95% CI, 0.29 to 0.66; $p < 0.001$; Supplementary Figure S6) decreased more significantly after a 6-month follow-up. A significant reduction in the incidence of ascites was reported in the probiotic group compared to the placebo or standard treatment (RR = 0.55; 95% CI, 0.41 to 0.74; $p < 0.001$), but there was no difference in abdominal pain, bloating, constipation, or other adverse events between groups (Figure 7).

According to the pooled result of adherence, the nonadherent rate was 6.75% in the probiotic group, whereas it was 6.4% in the control group, showing no significant difference between groups (Supplementary Figure S7).

3.5 Probiotics potentially improve liver function in patients with liver cirrhosis

The probiotic group demonstrated a statistically significant reduction in Model for End-Stage Liver Disease (MELD) scores compared with the control group (SMD = −0.57; 95% CI, −0.85 to −0.30; $p < 0.001$; Figure 8). The measurements of MELD containing international normalized ratio (INR), creatinine, and total bilirubin (TBIL) were shown in Supplementary Figure S8. However, the serum sodium levels of the probiotic group were still significantly lower than those of the control group (Supplementary Figure S9). And there was no difference in another liver function parameters in the blood (Supplementary Figure S10) and the Child-Turcotte-Pugh (CTP) classification (Supplementary Figure S11) between the probiotic group and the control group. The levels of liver function parameters were tested at different treatment time points, and the results showed that

TABLE 1 Study characteristics of the included studies.

Author, Year [Ref]	Country	Study period	Target population	Interventions of treatment group (sample size)	Treatment duration	Study duration	Interventions of control group (sample size)	Main findings
Agrawal A, 2012	India	2008.10–2009.12	Consecutive cirrhotic patients recovered from HE	Probiotics: Lactobacillus, Bifidobacterium, and *Streptococcus salivarius* subsp. thermophilus (*n* = 77)	3 months	12 months	No treatment (*n* = 78)	HE reversal, safety and tolerability, mortality.
Bajaj J S, 2008	USA	2005.10–2007.1	Nonalcoholic MHE cirrhotics	Probiotic yogurt: *S. thermophilus*, *L. bulgaricus*, *L. acidophilus*, Bidobacteria, and *L. casei* (n = 17)	2 months	2 months	No treatment (*n* = 8)	HE reversal, safety and tolerability, liver function, quality of life, inflammatory cytokines change.
Bajaj J S, 2014	USA	NA	Cirrhosis with MHE	Probiotic: Lactobacillus GG (LGG) (*n* = 14)	2 months	2 months	Placebo (*n* = 16)	Safety and tolerability, inflammatory cytokines change.
Dhiman R K, 2014	India	2010.1–2012.9	Cirrhosis recovered from HE	Probiotic: VSL#3 (*n* = 66)	6 months	6 months	Placebo (*n* = 64)	Safety and tolerability, mortality.
Efremova I, 2024	Russia	NA	Cirrhosis	Probiotic: S. boulardii CNCM I-745 (*n* = 20)	3 months	2 years	Placebo (*n* = 13)	Safety and tolerability, liver function, mortality.
Gupta N, 2013	India	NA	Cirrhotic patients having large esophageal varices	Probiotic: VSL#3 (*n* = 31)	2 months	2 months	Placebo (*n* = 32)	Safety and tolerability.
Horvath A, 2016	Austria	2012.7–2013.9	Cirrhosis	Probiotic: Bifidobacterium, Lactobacillus, and Lactococcus (*n* = 44)	6 months	12 months	Placebo (*n* = 36)	Safety and tolerability, liver function.
Jayakumar S, 2013	Canada	NA	Decompensated cirrhosis	Probiotic: VSL#3 (n = 7)	2 months	2 months	Placebo (n = 8)	Liver function.
Koga H, 2013	Japan	2005.10–2006.10	Alcoholic cirrhosis	Probiotic: beverage Yakult 400 (Y400) (*n* = 18)	2 weeks	1 month	Placebo (*n* = 19)	Effect on gut flora.
Liu Q, 2004	China	NA	Cirrhosis with MHE	Synbiotic preparation: consisiting of 4 bacteria along with fermentable fiber (*n* = 20)	1 month	1 month	Fermentable fiber (*n* = 20)	HE reversal, liver function, effect on gut flora, inflammatory cytokines change.
Loguercio C, 1987	Italy	NA	Cirrhosis	Probiotic: Enterococcus SF68 (*n* = 20)	10 days	20 days	Lactulose (*n* = 20)	HE reversal.
Loguercio C, 1995	Italy	NA	Cirrhotic patients with HE	Probiotic: Enterococcus SF68 (*n* = 21)	3 months	3 months	Lactulose (*n* = 19)	HE reversal.

(Continued)

TABLE 1 (Continued)

Author, Year [Ref]	Country	Study period	Target population	Interventions of treatment group (sample size)	Treatment duration	Study duration	Interventions of control group (sample size)	Main findings
Lunia M K, 2014	India	2012.1–2013.3	Cirrhosis	Probiotic: VSL#3 ($n = 86$)	3 months	3 months	Standard treatment ($n = 74$)	HE reversal, safety and tolerability, mortality.
Macnaughtan J, 2020	UK	NA	Cirrhosis	Probiotic: *Lactobacillus casei* Shirota ($n = 44$)	6 months	6 months	Placebo ($n = 43$)	Safety and tolerability, quality of life.
Manzhalii E, 2022	Ukraine	2017.1–2020.3	Cirrhosis with MHE	Probiotic: *Escherichia coli* Nissle 1917 strain ($n = 15$)	1 month	1 month	(1)Lactulose ($n = 15$) (2)Rifaximin ($n = 15$)	HE reversal.
Maslennikov R, 2022	Russia	NA	Consecutive cirrhosis	Probiotics:Saccharomyces boulardii ($n = 24$)	3 months	3 months	Placebo ($n = 16$)	HE reversal, safety and tolerability, liver function.
Mittal V V, 2011	India	2007.10–2009.10	Cirrhosis with MHE	Probiotics: subtype not available ($n = 40$)	3 months	3 months	Standard treatment ($n = 40$)	HE reversal, safety and tolerability.
Pande C, 2012	India	2005.4–2007.8	Cirrhotic patients with ascites	Probiotics: *E. faecalis* JPC, *C. butyricum*, B. mesentericus JPC, *Bacillus coagulans* ($n = 55$)	6 months	6 months	Placebo ($n = 55$)	Safety and tolerability, mortality.
Pereg D, 2011	Israel	NA	Cirrhosis	Probiotic: Lactobacillus, Bifidobacterium, and Streptococcus ($n = 20$)	6 months	6 months	Placebo ($n = 20$)	HE reversal, safety and tolerability, liver function.
Pratap Mouli V, 2015	India	2009.10–2012.6	Cirrhosis with MHE	Probiotic: VSL#3 ($n = 33$)	2 months	2 months	Lactulose ($n = 40$)	HE reversal, safety and tolerability, mortality.
Ramachandran G, 2023	India	2021.7–2022.10	Cirrhosis	Probiotics: VSL#3 ($n = 108$)	6 weeks	6 weeks	Placebo ($n = 107$)	Safety and tolerability, liver function, quality of life, mortality.
Roman E, 2019	Spain	2013.2–2016.3	Consecutive outpatients with cirrhosis	Probiotic: Streptococcus, Bifidobacterium, Lactobacillus ($n = 18$)	3 months	5 months	Placebo ($n = 18$)	Safety and tolerability, liver function, quality of life, mortality.
Saji S, 2011	India	NA	Cirrhosis with MHE	Probiotic: Lactobacillus, Bifidobacterium, and Sacharomyces ($n = 21$)	1 month	1 month	Placebo ($n = 22$)	Safety and tolerability.
Sharma K, 2014	India	2009.8–2010.8	Cirrhosis with MHE	Probiotics ($n = 32$)	2 months	2 months	Placebo ($n = 30$)	HE reversal, mortality.
Sharma P, 2008	India	2005.2–2006.8	Cirrhosis with MHE	Probiotics: *Streptococcus faecalis*, *Clostridium butyricum*, Bacillus mesentricus, lactic acid bacillus ($n = 35$)	1 month	1 month	Lactulose ($n = 35$)	HE reversal, liver function.

(Continued)

TABLE 1 (Continued)

Author, Year [Ref]	Country	Study period	Target population	Interventions of treatment group (sample size)	Treatment duration	Study duration	Interventions of control group (sample size)	Main findings
Shavakhi A, 2014	Iran	2012.6–2012.10	Cirrhosis with MHE	Synbiotics: Probiotic and Lactulose ($n = 19$)	2 weeks	10 weeks	Lactulose+Placebo ($n = 21$)	Safety and tolerability.
Shi J, 2023	China	2020.8–2021.8	Cirrhosis with MHE	Synbiotics: Probiotic and Lactulose ($n = 44$)	2 weeks	2 weeks	Lactulose ($n = 44$)	HE reversal, liver function, inflammatory cytokines change.
Xia X, 2018	China	NA	Cirrhosis with MHE	Probiotics: *Clostridium butyricum* and *Bifidobacterium infantis* (n = 30)	3 months	3 months	Standard treatment ($n = 37$)	HE reversal, safety and tolerability, liver function.
Zhao XH, 2013	China	NA	Cirrhosis with MHE	Probiotic ($n = 40$)	1 month	1 month	Placebo ($n = 40$)	HE reversal, safety and tolerability.
Ziada DH., 2013	Egypt	2010.3–2012.1	Cirrhosis with MHE	Probiotic: L. acidobacillus acidophilus ($n = 30$)	1 month	1 month	Lactulose ($n = 30$)	HE reversal, liver function, effect on gut flora.

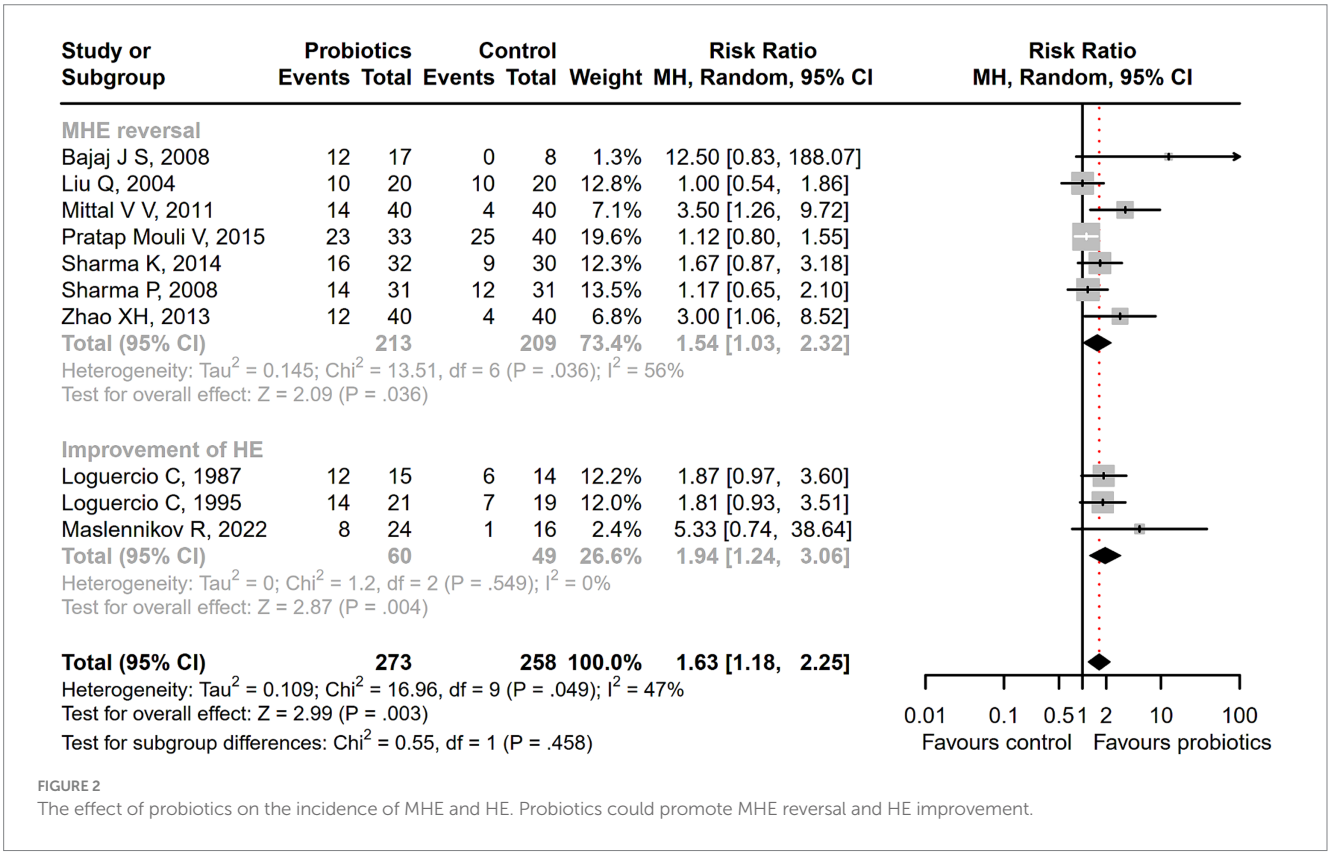

FIGURE 2
The effect of probiotics on the incidence of MHE and HE. Probiotics could promote MHE reversal and HE improvement.

as the intervention time prolonged, the levels of parameters showed a continuous downward trend, but statistically, it was not significant (Supplementary Figure S12). Sensitivity analysis showed the overall effect size of INR would be impacted by removing a single effect size (Supplementary Figure S13).

3.6 Probiotics induce favorable changes on quality of life and gut flora

After receiving probiotic treatment, the quality of life score of patients with cirrhosis significantly improved (SMD = 0.51; 95% CI,

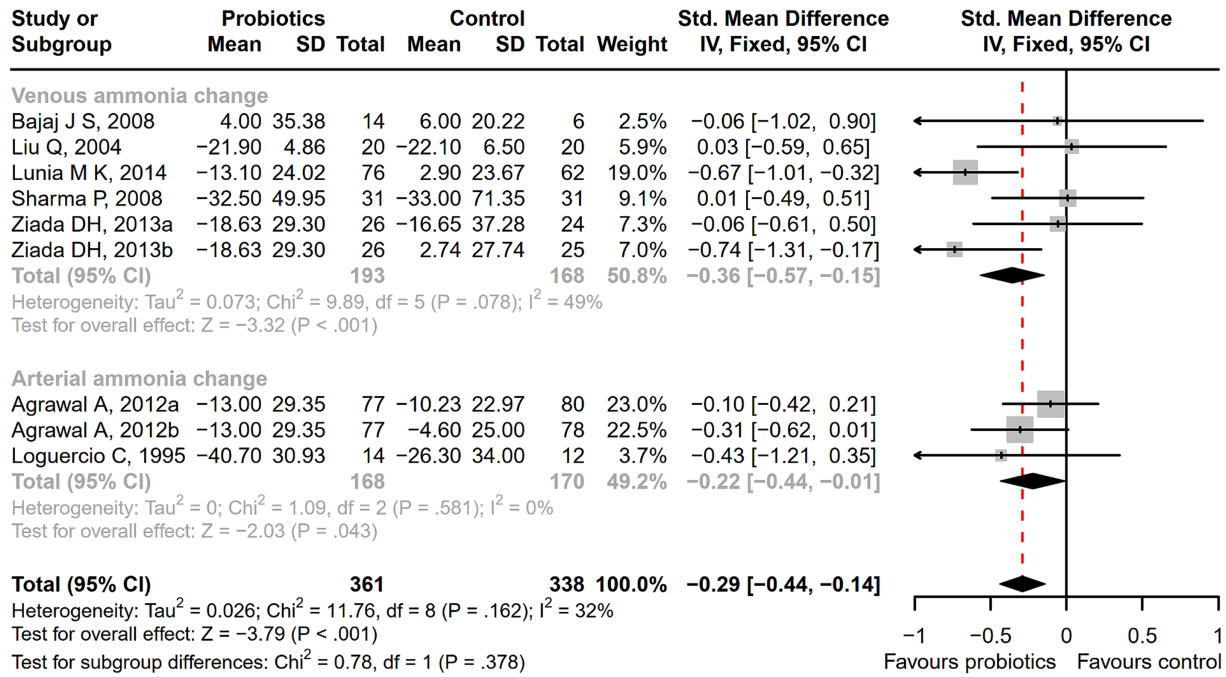

FIGURE 3
The effect of probiotics on the ammonia level. There was a significant decrease in both venous and arterial ammonia level among the patients receiving probiotics.

0.27 to 0.75; $p < 0.001$; Figure 9). The numbers of the *Lactobacillus* group were significantly increased after probiotic treatment (SMD = 1.67; 95% CI, 1.28 to 2.06; $p < 0.001$), while the numbers of *Enterobacteriaceae*, *Bifidobacterium*, *Enterococcus*, *Bacteroidaceae*, and *Fusobacterium* did not differ significantly between the probiotic and control groups (Figure 10). Sensitivity analysis of quality of life (Supplementary Figure S14) showed that the overall effect size could be influenced by removing a single effect size, whereas the overall effect size remained unaffected by the removal of a single effect size in the results of gut flora (Supplementary Figure S15).

3.7 Probiotics have no significant effect on inflammatory cytokines expression and mortality

Among cirrhotic patients receiving probiotics, there was a numerical but not prominent decrease in serum inflammatory cytokine expression, including endotoxin, interleukin (IL)-6, and tumor necrosis factor (TNF)-α (Supplementary Figure S16). Meanwhile, there was a numerical but non-significant decline in mortality (Supplementary Figure S17). The overall effect size was not influenced by removing a single effect size, according to the sensitivity analysis of IL-6 (Supplementary Figure S18).

3.8 Quality assessment and publication bias

Two studies reported a low overall risk of bias. High risk of bias was most represented in the domains of blinding of participants and personnel, and blinding of outcome assessment (Supplementary Figure S19). The detailed support for the judgment of the risk of bias in each included study was shown in Supplementary Table S4. Egger' s regression test or Peter's test showed there was no publication bias in the results of the main findings containing HE reversal, safety and tolerability of probiotics, liver function, and gut microbial taxonomy ($p > 0.05$) (Supplementary Figure S20).

4 Discussions

In recent years, numerous clinical trials have employed probiotics as a treatment for various liver diseases, encompassing conditions such as liver cirrhosis (32), nonalcoholic fatty liver disease (NAFLD) (55), and HE (56). Probiotic therapy has been systematically analyzed for its effects on NAFLD and HE, and previous reviews have demonstrated its efficacy as a therapeutic strategy (57, 58). While there have been synthesis analyses examining the effects of probiotics in patients with liver cirrhosis, these analyses were either limited to cirrhotic patients with MHE (18) or were not conducted exclusively based on randomized clinical trials (20). The available evidence regarding the effects of probiotics on the course of cirrhosis is limited. This is a critical aspect of potentially reversing the onset of cirrhosis in its early stages and preventing further disease progression. This systematic review and meta-analysis comprehensively investigated the effectiveness of probiotic interventions in cirrhosis through the synthesized analysis of RCTs, representing the pinnacle of the evidence pyramid. The findings indicated that probiotics may mitigate the negative effects of cirrhosis by reversing cirrhotic HE, potentially improving liver function, and fostering favorable changes in quality of life and gut microbial taxa. Moreover, probiotic interventions appeared to exhibit a higher level of safety and tolerability.

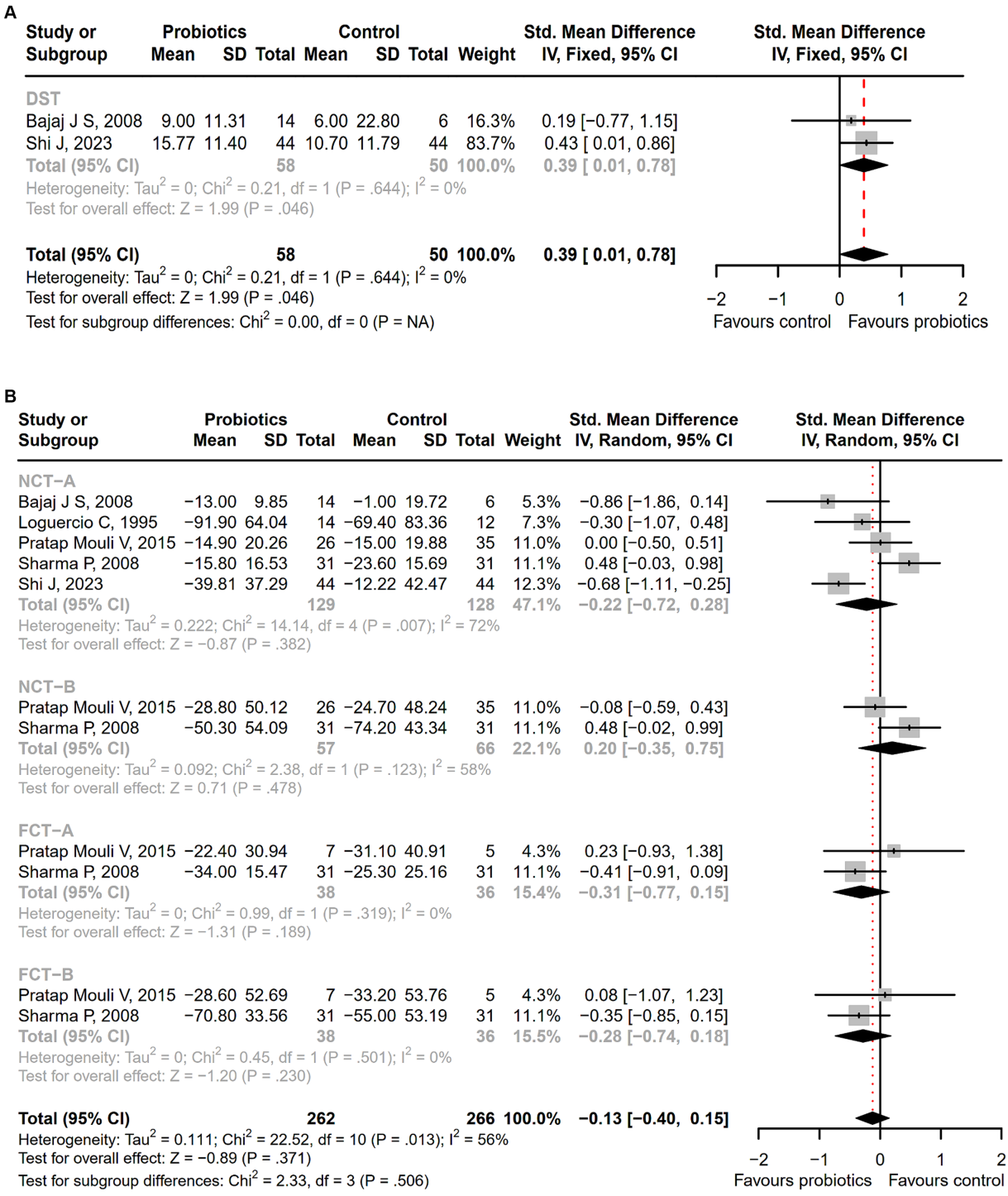

FIGURE 4
The forest plot of neuropsychometric assessments. **(A)** DST; **(B)** NCT-A, NCT-B, FCT-A, FCT-B. Notable higher DST scores were shown in the probiotic group.

HE is often a complication of advanced liver dysfunction, especially cirrhosis, causing mental confusion due to the buildup of toxins in the brain. One of the toxins affecting the brain is ammonia. Elevated ammonia levels are believed to be the culprit in the pathogenesis of HE (59). This systematic review and meta-analysis revealed that, in comparison to treatment measures in the control group such as lactulose and placebo, probiotic intervention had a notably beneficial effect on reducing ammonia levels in the blood. A neuropsychometric test is an important tool to diagnose different grades of HE, including DST, block design test (BDT), NCT-A, NCT-B, line tracing test (LTT), and serial dotting test (SDT) (60). This study demonstrated an enhancement in the neuropsychometric status of cirrhotic patients with HE after receiving

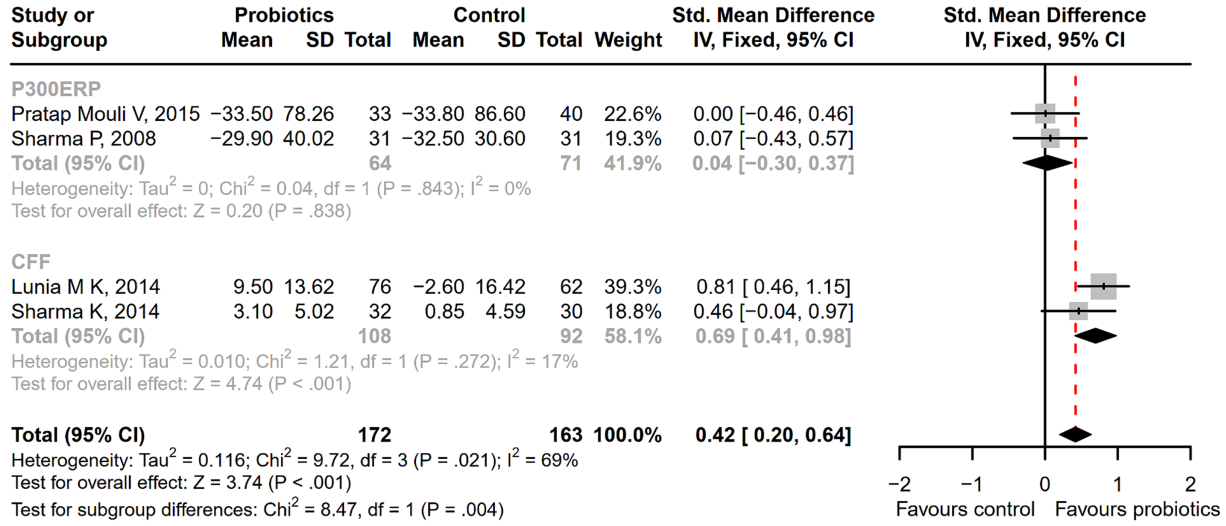

FIGURE 5
The forest plot of neurophysiological tests of P300 auditory event-related potential (P300ERP) and critical flicker frequency (CFF). A significant improvement in critical flicker frequency (CFF) was observed in the probiotic group.

probiotics, as evidenced by lower DST scores. And the significant improvements in CFF prove enhancements in the neurophysiological status among cirrhotic patients after receiving probiotics. These results suggest that probiotics have the potential to ameliorate the condition of patients with HE. This is further supported by our meta-analysis, which revealed a significant reversal of MHE and improvement of HE among patients in the probiotic group. Additionally, VSL#3, as a commonly used probiotic for repairing the intestinal barrier, has been proven to play a positive role in the treatment of multiple diseases (61, 62). Our research also found that VSL#3 could play an effective role in improving HE, suggesting it might be considered as a priority choice for probiotic treatment to reverse HE in the future.

Probiotics are among the most commonly used dietary supplements. It showed good tolerability, a low attrition rate, and no serious adverse reactions in many clinical trials for a variety of diseases (63, 64). Although many probiotics are considered safe, with increasing usage among cirrhotic patients in clinics, there may be a greater need to assess their safety and tolerability. Our study revealed a lower incidence of adverse events or serious adverse events among patients receiving probiotics compared to those receiving lactulose, placebo, or standard treatment. This suggests good tolerability and a high likelihood of safety of probiotics in cirrhosis. There was no significant difference in nonadherence rates between the groups, indicating that patients were able to tolerate and remain compliant with probiotic therapy. This finding is conducive to the further promotion and expansion of the use of probiotics.

Liver cirrhosis is characterized by liver scarring, impaired liver function, and other side effect (65). The MELD score and CTP classification are extensively employed for the evaluation of liver function, where a higher score indicates more pronounced functional impairment. They have been widely used for the assessment of prognosis in liver cirrhosis (66). Our study revealed no discernible difference in CTP classification between the intervention and control groups. This finding may not offer robust evidence regarding the effect of probiotic intervention, considering that the parameters of the CTP classification incorporate subjective indicators such as ascites and encephalopathy. In contrast, MELD scores are calculated based on objective indicators, including INR, TBIL, and creatinine, demonstrating enhanced predictive capabilities for liver function and providing a reliable assessment of cirrhosis severity (67). In this systematic review and meta-analysis, a reduction in the MELD score was observed after probiotic intervention. However, the statistical significance of the changes in MELD scores may not have reached clinical significance. Additionally, some liver function parameters, such as ALT and AST, did not exhibit statistically significant changes. This suggests that probiotics might have the potential to improve liver function among cirrhosis patients, but the clinical improvement effects still require further confirmation. The insufficient intervention time might also be an important reason for the poor clinical improvement of the indicators.

This study also investigated the expression levels of serum sodium, an important indicator reflecting the liver function status among cirrhotic patients. In patients with cirrhosis, the abnormal activity of the antidiuretic hormone system may lead to a disruption in sodium metabolism, which could result in the occurrence of hyponatremia (68). This study found that hyponatremia did not improve after probiotic treatment. This phenomenon may be attributed to the insufficient adoption of an evidence base for this meta-analysis, potentially impacting the pooled outcomes adversely. Moreover, in this study, the intervention duration of the existing studies for analyzing the effects of probiotics on serum sodium was less than 3 months, consistent with the assessment time of MELD scores. An important finding observed from this study showed that at least 3 months of probiotic intervention were required for yielding favorable outcomes on indicators including ammonia levels and the incidence of adverse events. With the extension of the follow-up time, the impact of probiotics became more significant. This suggests that a certain duration is necessary for probiotics to exert their beneficial effects. And as the intervention and follow-up time prolong, the efficacy of probiotics becomes increasingly significant. Therefore, due to the limitations of the existing evidence base, we failed to identify significant clinical improvement effects in liver function among cirrhotic patients after probiotic intervention. However, the statistically significant changes in MELD scores still suggest that probiotics have the potential

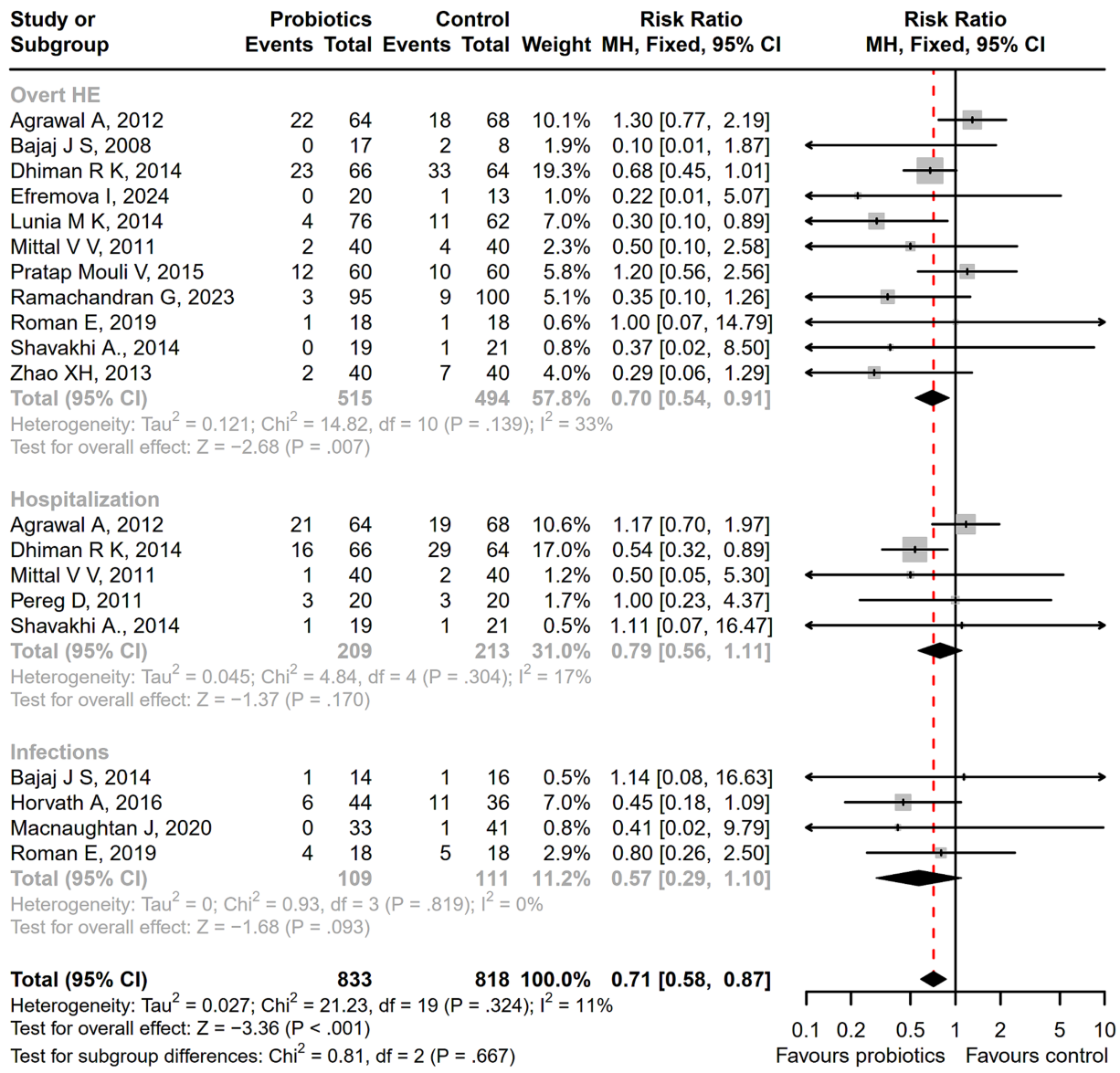

FIGURE 6
The forest plot of the serious adverse events incidence. There was a significant lower incidence of overt HE, hospitalization, and infections among patients receiving probiotic treatment, compared with the control treatment.

to enhance liver function. Future probiotic intervention studies could consider concentrating on these indicators to furnish more evidence regarding liver function changes among cirrhotic patients.

The heightened secretion of endotoxin, a bacterial product, induced by an imbalance in the gut microbiota among patients with cirrhosis, results in liver damage (69). Endotoxin can exacerbate liver damage by amplifying the release of inflammatory factors (70). Therefore, regulating the gut microbial profile is crucial for preventing cirrhosis progression. The results of this study revealed favorable alterations in the stool microbial profile, characterized by an increase in beneficial bacteria *Lactobacillus*. The changes could contribute to the reduction of endotoxin levels and inflammatory factors such as TNF-α or interleukin (IL)-6, aligning with the findings of this systematic review and meta-analysis. However, the results of the study showed that some intestinal flora and inflammatory cytokine disturbances were not significantly restored, which might also be the reason why the liver function of cirrhotic patients did not improve clinically after probiotic intervention.

Quality of life in cirrhotic patients is significantly impaired by the disease manifestations and complication (71, 72). Our study found a notable enhancement in the quality of life in cirrhosis patients, which might be correlated with the decrease in the incidence of adverse events after receiving probiotic treatment. However, we failed to detect a significant reduction in mortality. This might be attributed to the fact that the effects of probiotics on this indicator require an extended follow-up time to be apparent. Most of the included studies had a follow-up duration of around 3 months, which might not be sufficient to observe significant improvement effects. Therefore, future studies could extend the follow-up period to observe more objective outcomes that support the beneficial effects of probiotics.

Despite the significance of this systematic review and meta-analysis, several limitations need to be acknowledged. Firstly, among the 30

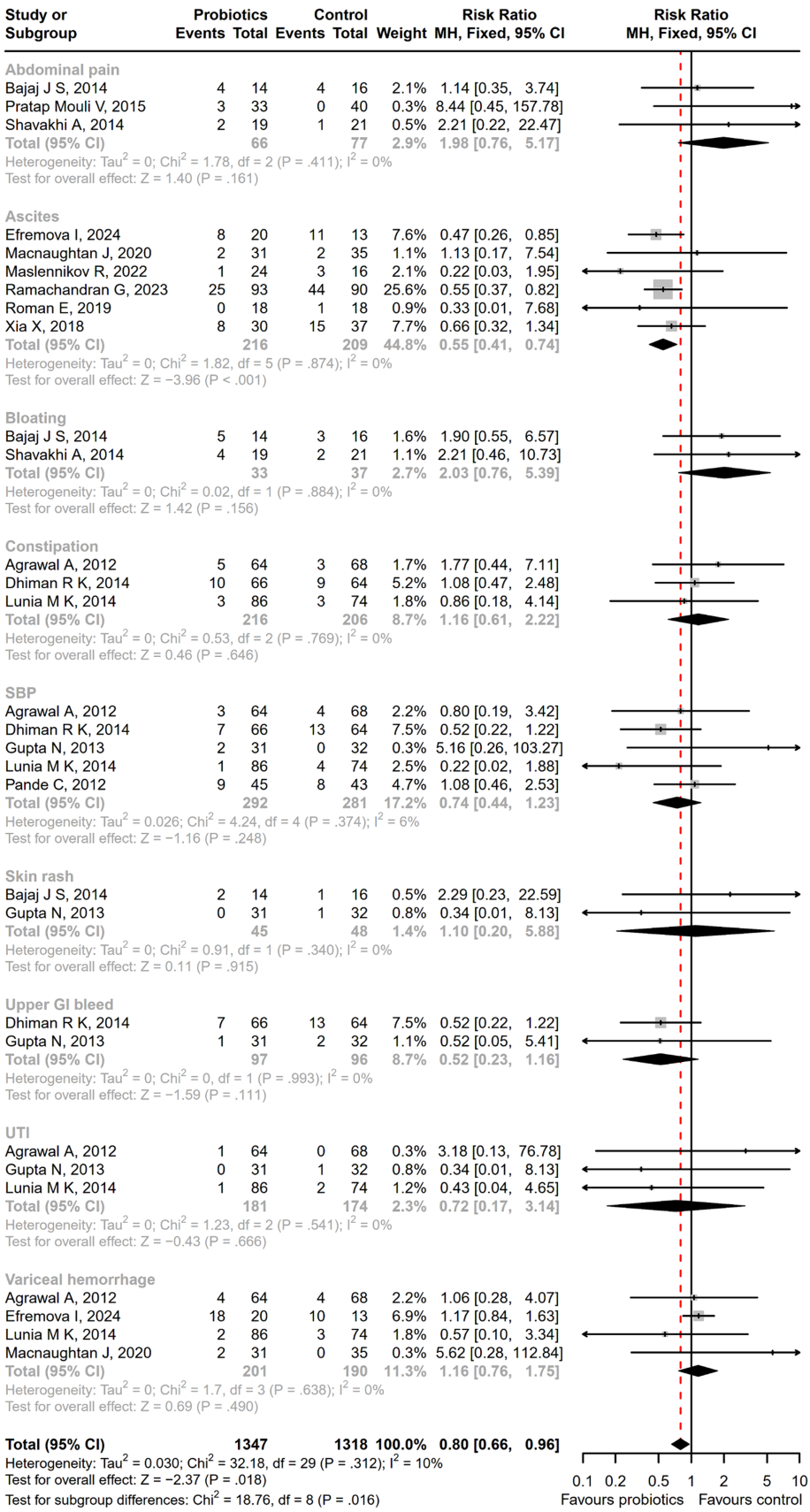

FIGURE 7
The forest plot of the adverse events incidence. There was a significant lower incidence of ascites in the probiotic group, but no difference in the other adverse events such as abdominal pain, bloating, and constipation between groups.

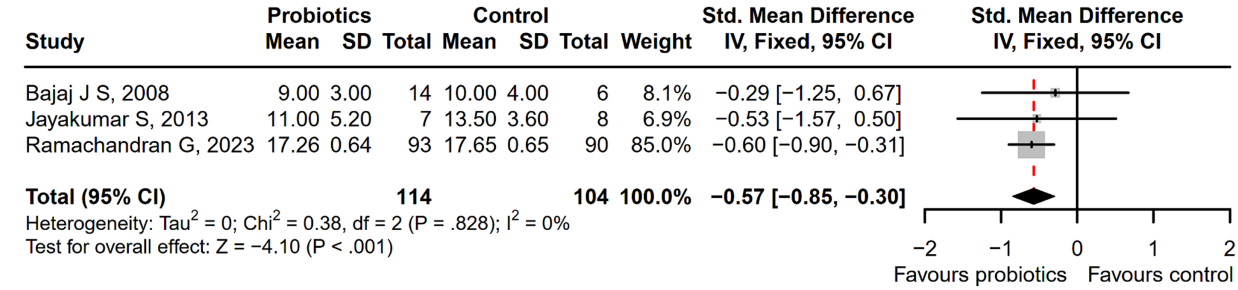

FIGURE 8
The effect of probiotics in MELD scores. The probiotics could significantly reduced the MELD scores, compared with control treatment.

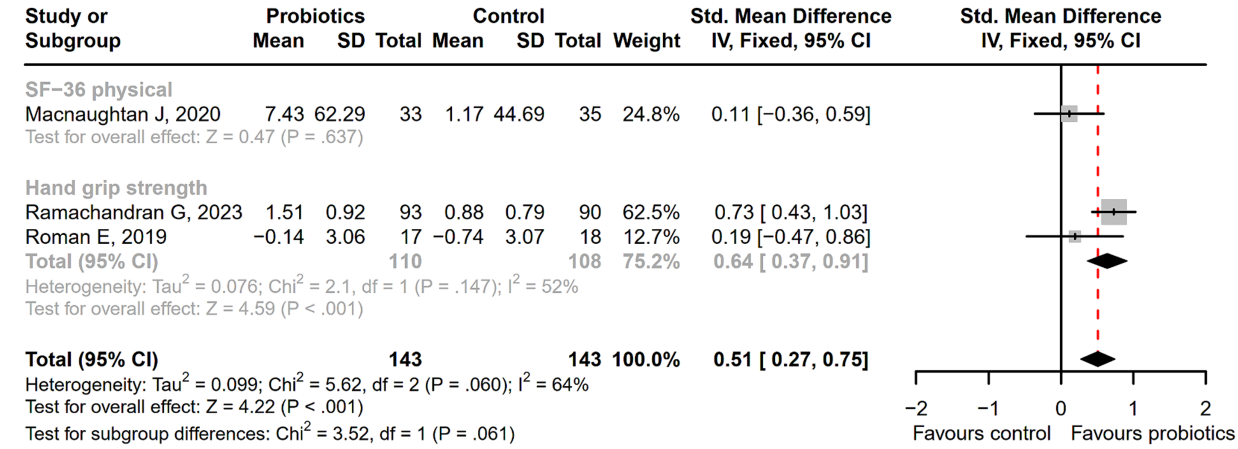

FIGURE 9
The forest plot of quality of life. The quality of life score of cirrhotic patients significantly improved in the probiotic group.

studies included, only 2 exhibited a low risk of bias across all seven domains, while the remaining 28 showed a high or unclear risk of bias for at least one bias domain. Secondly, there is a scarcity of available evidence base on the intervention effect of various types of probiotics or different duations of treatment in cirrhosis, preventing a more comprehensive comparison of the impact among probiotics or treatment durations on cirrhosis. Lastly, although RCTs were incorporated in this study, and the results obtained possessed a high level of evidence, some results lacked a sufficient number of included studies for a comprehensive meta-analysis, limiting the depth of our analysis. Future studies should strive to address these gaps, maximizing the utilization of probiotics to promote cirrhosis reversal and prevention.

5 Conclusion

This systematic review and meta-analysis provides compelling evidence supporting the benefits of probiotics in cirrhosis. Probiotics contribute to the reduction of ammonia levels and the improvement of neuropsychometric or neurophysiological status, leading to the reversal of HE associated with cirrhosis. They exhibit higher safety and tolerability, as evidenced by a significant lower incidence of serious adverse events compared with the control treatment. Probiotics demonstrate the potential to enhance liver function by down-regulating the MELD score. Moreover, they induce favorable changes in gut flora and quality of life. Therefore, probiotics emerge as a promising intervention for reversing the onset of cirrhosis and preventing disease progression.

Data availability statement

All data relevant to the study are included in the article or uploaded as Supplementary information.

Author contributions

XY: Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. LLe: Data curation, Investigation, Methodology, Software, Writing – original draft. WS: Data curation, Methodology, Software, Validation, Writing – review & editing. XL: Funding acquisition, Methodology, Resources, Validation, Writing – review & editing. XH: Data curation, Methodology, Writing – original draft. LLa: Data curation, Methodology, Software, Writing – original draft. JL: Methodology, Software, Writing – original draft. QL: Data curation, Methodology, Writing – original draft. WL: Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing. JY: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing.

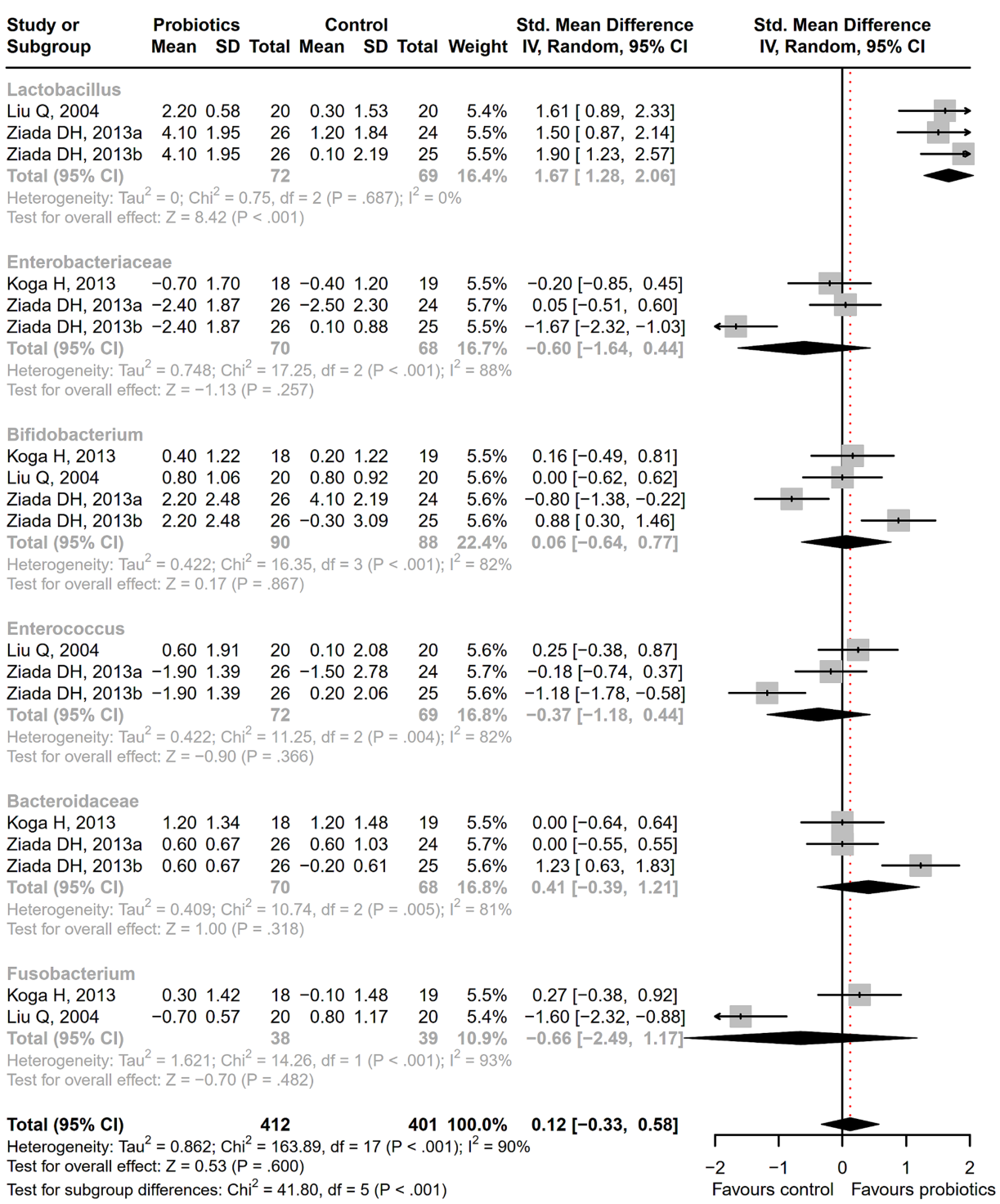

FIGURE 10
The effect of probiotics on gut flora. The numbers of *Lactobacillus* group were significantly increased.

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Conflict of 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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1379333/full#supplementary-material

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Case report: Rapid development of acute symptomatic portal vein system thrombosis after endoscopic variceal therapy in a patient with liver cirrhosis

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Acute portal vein thrombosis (PVST), a serious complication of liver cirrhosis, is characterized as abdominal pain secondary to intestinal ischemia, and even intestinal necrosis. Anticoagulation is recommended for the treatment of acute PVST, but is often postponed in cirrhotic patients with acute variceal bleeding or those at a high risk of variceal bleeding. Herein, we reported a 63-year-old male with a 14-year history of alcoholic liver cirrhosis who developed progressive abdominal pain related to acute portal vein and superior mesenteric vein thrombosis immediately after endoscopic variceal ligation combined with endoscopic cyanoacrylate glue injection for acute variceal bleeding. Fortunately, acute PVST was successfully recanalized by the use of low molecular weight heparin. Collectively, this case suggests that acute symptomatic PVST can be secondary to endoscopic variceal therapy in liver cirrhosis, and can be safely and successfully treated by anticoagulation.

KEYWORDS

portal vein system thrombosis, superior mesenteric vein thrombosis, endoscopic variceal treatment, anticoagulation therapy, liver cirrhosis

1 Introduction

Portal vein system thrombosis (PVST), mainly including portal vein thrombosis (PVT), superior mesenteric vein (SMV) thrombosis, and splenic vein thrombosis, is a common complication of liver cirrhosis (1), with a prevalence of 11.18%–16.91% and an incidence of 8.16%–12.92% (2). While PVST is often asymptomatic in liver cirrhosis and even transient (3), a subset of PVST patients may develop acute and progressive manifestations related to intestinal ischemia, such as abdominal pain, and even intestinal necrosis (4).

The occurrence of PVST is generally multifactorial. Its local risk factors often include splenectomy, splenic arterial embolization, and intra-abdominal surgery (5). But it remains controversial about whether endoscopic variceal therapy (EVT) is a risk factor for PVT among studies. Politoske et al. (6) concluded that the incidence of PVT following EVT was similar to that in unselected patients with cirrhosis and portal hypertension. By comparison, accumulative evidence from our group and others have supported EVT as a potential risk factor for the development of PVST in liver cirrhosis (7, 8).

Anticoagulation is recommended for the treatment of PVST in liver cirrhosis (9), considering its efficacy in achieving portal vein recanalization (10). However, anticoagulation is often postponed or avoided in cirrhotic patients with acute variceal bleeding (AVB) or those at a high risk of bleeding. Until now, the evidence regarding initiation of anticoagulation is still insufficient in such patients.

Herein, we reported a case of liver cirrhosis where acute symptomatic PVST developed soon after EVT, but was successfully recanalized by anticoagulation.

2 Case description

On 23 November 2020, a 63-year-old male admitted to our department due to hematemesis and melena for a duration of 4 days. Upon admission, the patient did not have abdominal pain, distension, or fever. He was diagnosed with alcoholic liver cirrhosis in 2006. He had repeatedly undergone EVT for gastroesophageal variceal bleeding since 2012. He was also diagnosed with hepatocellular carcinoma (HCC) in 2013 and had been repeatedly treated with transcatheter arterial chemoembolization (TACE) since then. The last TACE procedure was performed on 6 November 2020, and his liver lesion was stable at this admission. He was treated with partial splenic embolization for hypersplenism in 2014. Notably, before this admission, he performed contrast-enhanced computed tomography (CT) scans on 7 November 2020, which revealed only partial thrombosis within the main portal vein (**Figure 1A**).

On November 27, the patient underwent EVT, including variceal ligation for severe esophageal varices and injection of a mixture of cyanoacrylate and glucose (1 ml 50% glucose + 1 ml cyanoacrylate + 1 ml 50% glucose) for severe gastric varices with adherent clot. At the same day, the patient's general condition remains stable without abdominal pain or fever. On November 29, he developed acute persistent abdominal pain and mild fever (37.5°C) with an elevated D-dimer level of 17.06 mg/L (**Table 1**). Emergency abdominal CT angiography (**Figure 1B**) suggested acute extensive thrombosis extended to the SMV. Considering that active gastrointestinal bleeding stopped with a stable hemoglobin level and esophageal and gastric varices had been treated with EVT, anticoagulation therapy was immediately initiated after the patient and his family members sufficiently understood the risk of anticoagulation and the patient's wife signed the written informed consents. Subcutaneous injection of low molecular weight heparin (LMWH) with a dosage of 5,000 IU bid was immediately administered. Subsequently, abdominal pain and fever gradually resolved within 2 days. Contrast-enhanced CT scans were repeated on 19 January 2021, showing recanalization of SMV thrombosis and partial thrombosis within the main portal vein (**Figure 1C**). LMWH was maintained for 6 months and then switched to oral rivaroxaban. The patient remained asymptomatic without recurrent thrombosis until melena recurred on 4 August 2023. He underwent tissue adhesive injection for gastric varices at our department. Oral rivaroxaban was re-titrated after EVT. At the last follow-up visit on 14 December 2023, he remained stable without rebleeding events.

3 Discussion

3.1 PVST after EVT

The pathogenesis of thrombus formation should be classical Virchow's triad: decreased blood flow velocity, vascular endothelial injury, and hypercoagulable state (11). In liver cirrhosis, increased portal pressure can reduce blood flow velocity, which may be a main risk factor of PVST development (12). Similarly, there is an increased incidence of PVT with deterioration of liver function (13). In our case, it can be proposed that EVT induces an alteration of portal hemodynamics, leading to a transient increase in portal pressure and an increased risk of PVT. However, the correlation between EVT and PVT is still debated among literature (6–8). Our case had been diagnosed with partial PVT which was asymptomatic, but experienced acute symptomatic PVST extending to the SMV within only 2 days after EVT. Furthermore, he had imaging evidence before and after EVT, which clearly indicates its impact on acute thrombus extension. Recent evidence also supports a causal effect estimation of EVT, particularly endoscopic sclerotherapy (7), variceal ligation, and variceal ligation combined with endoscopic cyanoacrylate glue injection (8), with the risk of PVST. The underlying mechanism of PVST formation after EVT needs to be further explored. Regardless, the risk of PVST should be closely screened in patients undergoing EVT.

Certainly, our case also involves other possible factors contributing to thrombus formation, including prior history of HCC, TACE, and splenic arterial embolization (5). However, they might be associated with partial PVT before this admission, rather than acute SMV thrombosis at this admission.

Our case also had elevated WBC and C-reactive protein (CRP) levels after EVT, which was in parallel with the development of acute PVT event (**Figure 2**). This phenomenon suggested that thrombo-inflammation should be the potential mechanism of PVT in our case. Liver cirrhosis is associated with activation of systemic inflammation, which may increase the risk of PVST (14, 15). It has been shown that inflammatory markers, such as CRP, tumor necrosis factor α, procalcitonin, and interleukin 6, were positively correlated with PVT in cirrhotic patients (16, 17). In turn, thrombosis also exacerbates inflammation mediated by endothelial cells, leukocytes, and platelets (18). PVT can also directly occlude the portal vein lumen, slowing blood flow and increasing the chance of intestinal bacterial translocation, thereby raising the risk of systemic inflammation (19). Despite the role of local inflammation as a precipitating factor of thrombus formation has been well known (16), our case did not present with any inflammation-related manifestations before this acute PVST event. Instead, fever occurred after a diagnosis of PVST, indicating that local intestinal blood stasis should induce inflammation reaction. After anticoagulation, the patient's temperature gradually normalized without anti-inflammatory medications. Collectively, inflammation should be concomitant with acute PVST event, but may not be a risk factor for acute PVST.

Cancer itself can also cause the hypercoagulability in this patient, leading to a higher incidence of PVT (20). In patients with HCC, the development of PVT might be associated with various causes, including direct tumor compression, tumor secondary hypoxia, and circulating tumor cells (21). Furthermore, tumors can

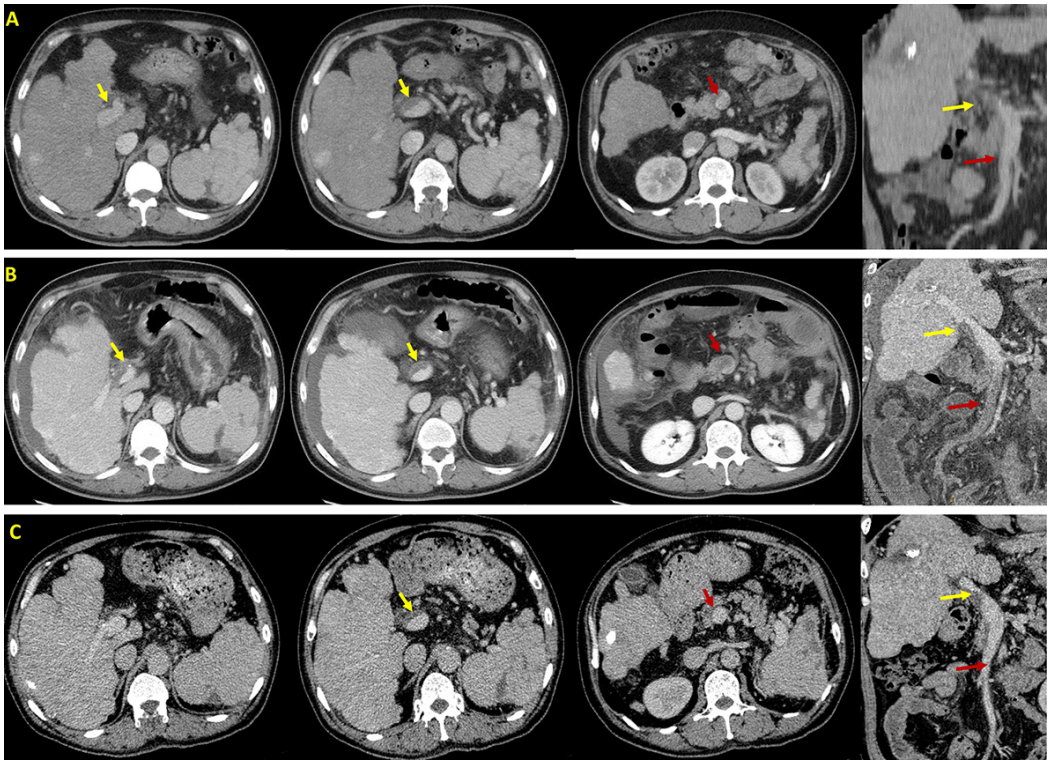

FIGURE 1
Axial and coronal contrast-enhanced computed tomography scans in this patient. **(A)** Before EVT, CT scans performed on 7 November 2020 demonstrated PVT (yellow arrow) without SMV thrombosis (red arrow). **(B)** After EVT, CT scans performed on 29 November 2020 demonstrated PVT (yellow arrow) with acute SMV thrombosis (red arrow). **(C)** After anticoagulation, CT scans performed on 19 January 2021 demonstrated that PVT remains stable (yellow arrow) and SMV thrombosis disappeared (red arrow).

increase inflammatory factors, such as tumor necrosis factor α, posing this patient at a hypercoagulable state (20, 22).

Impact of D-dimer on the development of PVT should not be neglected in this case. D-dimer level was slightly elevated upon admission, but significantly increased after EVT (**Figure 2**). The change of D-dimer level correlates positively with the progression of PVT. This is consistent with the findings of our previous meta-analysis that D-dimer serves as a predictive marker for PVT in cirrhosis, and postoperative D-dimer, rather than preoperative D-dimer, should be of significance on the development of PVT (23). This emphasizes the importance of monitoring D-dimer levels after EVT or surgery for earlier detection of PVT.

Another possibility should not be ignored that endoscopic cyanoacrylate injection caused glue migration, thereby inducing the development of PVST (24). Cyanoacrylate glue induced PVST, which is well-known, but rare, is reported in 2% patients who underwent endoscopic cyanoacrylate injection for gastric varices (25). But this possibility cannot be supported, because the SMV patency was immediately achieved following anticoagulation therapy in our case.

3.2 Anticoagulation for PVST

Anticoagulation is recommended as the first-line treatment for acute symptomatic PVST (9). According to the data from a meta-analysis, the pooled rate of overall bleeding, upper gastrointestinal bleeding, and major bleeding in patients with cirrhosis and PVST after anticoagulation was 10.3%, 3.2%, and 2.8%, respectively (7). Concerns about the risk of bleeding associated with anticoagulation often limit its use in patients with AVB. Notably, in our case, the onset of acute PVST followed a recent AVB event. Despite so, anticoagulation had to be immediately administered for acute symptomatic extensive PVST presenting with persistent abdominal pain secondary to intestinal ischemia to maximize the rate of portal vein recanalization. Finally, our case achieved a resolution of clinical symptoms and recanalization of SMV thrombosis after anticoagulation without any bleeding event. Thus, our case further confirms that once hemostasis is achieved, early anticoagulation is safe and effective in cirrhosis. This is consistent with the findings from a recent multi-centric randomized controlled trial by Gao et al. and a recent meta-analysis by our group (26, 27).

Thrombolytic therapy is an alternative choice of treatment for acute symptomatic PVT (28). As previously reported, it should be more effective (29, 30). However, it carries a potentially higher risk of bleeding (28). Therefore, it was not considered as the first-line choice in our current case with AVB following EVT. Transjugular intrahepatic portosystemic shunt should also be another choice in our case, if anticoagulation fails or is not feasible (31, 32).

According to the current practice guidelines for the diagnosis and treatment of PVT and deep vein thrombosis, the recommended dosage of LMWH should be 100 U/kg twice daily (9, 33). Our patient weighed approximately 60 kg. Thus, theoretically, LMWH should be given at a dosage of

TABLE 1 Laboratory tests of this patient.

Laboratory examination	Results			Unit	Normal range
	At admission (23/11/2020)	After EVT (29/11/2020)	After anticoagulation (6/12/2020)		
PT	14.8	**16.6**	**15.6**	s	11.5–14.5
INR	1.22	1.41	1.3	/	/
APTT	42.2	44.3	56.8	s	28.0–40.0
FIB	2.36	2.43	2.25	g/L	2.00–4.00
D-dimer	1.56	**17.06**	**3.81**	mg/L FEU	0.01–0.55
PLT	145	166	186	$\times 10^9$/L	125–350
WBC	4.3	**15.6**	4.5	$\times 10^9$/L	3.5–9.5
NEU	3.29	**13.2**	3.08	$\times 10^9$/L	1.8–6.3
RBC	3.77	4.38	3.95	$\times 10^{12}$/L	4.3–5.8
Hb	84	98	95	g/L	130–175
TBIL	14.6	22.3	16	μmol/L	5.1–22.2
ALT	7.3	5.27	4.92	U/L	9–50
AST	13.12	13.04	16.55	U/L	15–40
AKP	104.96	95.22	77.82	U/L	45–125
GGT	50.03	45.33	50.47	U/L	10–60
ALB	30.9	34.5	31.1	g/L	40–55
LIPA	**359**	41	NA	U/L	23–300
AMY	43	30	NA	U/L	30–110
CRP	11.04	**90.14**	**44.61**	mg/L	≤10

EVT, endoscopic variceal therapy; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; FIB, fibrinogen; PLT, platelet; WBC, white blood cell; NEU, neutrophils; RBC, red blood cell; Hb, hemoglobin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AKP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; ALB, albumin; LIPA, lipase; AMY, amylase; CRP, C-reactive protein; NA, not available. The bold values indicate significantly abnormal changes in the laboratory tests.

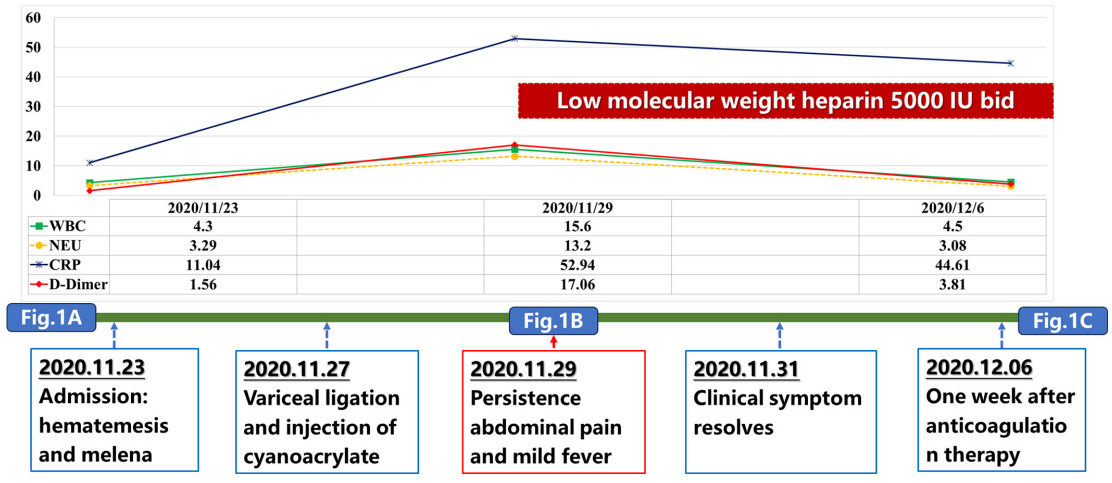

FIGURE 2
A time-line of this patient's disease course.

6,000 U subcutaneous injection every 12 h. However, our patient received LMWH at a dosage of 5000 U subcutaneous injection every 12 h. This was attributed to two considerations. First, he had recently experienced AVB before anticoagulation, raising concerns about the risk of rebleeding secondary to a therapeutic dosage of anticoagulation. Hence, we preferred to reduce the dosage of LMWH slightly. Second, the specific dosage of LMWH per syringe is 5,000 U at our hospital. Thus, it is also more convenient for our clinical practice, as compared to 6,000 U.

3.3 Follow-up

During the follow-up period, our case received long-term anticoagulation therapy without any adjustment of other regimens. Notably, there was a notable decrease in the frequency of bleeding events, including 11 AVB episodes within 8 years before anticoagulation, but only one re-bleeding episode 3 years after anticoagulation. This phenomenon is consistent with the findings of our meta-analysis that anticoagulation may decrease the incidence of variceal bleeding in cirrhotic patients with PVST to some extent (7). We speculate that this benefit results from the improvement of microvascular thrombosis and decrease of portal vein pressure after long-term anticoagulation therapy.

4 Conclusion

Our case emphasizes the necessity of screening for PVST after EVT in cirrhotic patients, and also supports the efficacy and safety of anticoagulation for PVST in the case of high-risk bleeding. Further cohort studies are very necessary to validate this conclusion.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was not required as this is a single case report and does not include identifiable data of the patient. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

RW: Writing – original draft, Writing – review & editing. XG: Writing – review & editing. FG: Writing – review & editing. YZ: Writing – review & editing. QL: Writing – review & editing. SJ: Writing – review & editing. XS: Writing – review & editing. XQ: Writing – original draft, Writing – review & editing, Conceptualization, Supervision.

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Conflict of 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. The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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The prevalence and characteristics of frailty in cirrhosis patients: a meta-analysis and systematic review

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Objectives: This study aimed to assess the prevalence of frailty in cirrhosis patients and the distribution of age, sex, and body mass index (BMI) in cirrhotic patients with frailty.

Methods: We performed a thorough literature search using PubMed, Embase, Web of Science, and the Cochrane Library from inception to 29 February 2024. The estimated prevalence with a 95% confidence interval (CI) was calculated with a random effect model. Subgroup analysis and sensitivity analysis were performed to assess the heterogeneity and characterize the distribution of age, sex, and body mass index (BMI) in cirrhotic patients. Publication bias was assessed by the funnel plot, Begg's test, and Egger's test.

Results: The 16 included studies, which were all observational, reported a prevalence of frailty in 8,406 cirrhosis patients ranging from 9 to 65%, and the overall estimated prevalence was 27% (95% CI: 21–33%; $I^2 = 97.7\%$, $P < 0.001$). This meta-analysis indicated that the estimated prevalence of frailty in cirrhosis patients was high, and compared to the non-frail cohort, the frail cohort tended to have a higher mean age, with a mean age of 63.3 (95% CI: 59.9, 66.7; $Z = 36.48$; $P < 0.001$), and a larger proportion of male patients with worse liver function, with a mean of 73.5% (95% CI: 71.4, 75.5%; $Z = 7.65$; $P < 0.001$), ND in the frail cohort, 54.8% (95% CI: 43.1, 66.5%; $P < 0.001$) and 23.4% (95% CI: 13.2, 33.7%; $P < 0.001$) were classified into Child-Pugh B and C, respectively. Meanwhile, the patients in the non-frail cohort are more likely to have a higher BMI, with a mean of 28.4 (95% CI: 24.1, 32.7; $Z = 13.07$; $P < 0.001$).

Conclusion: The current study suggests that cirrhosis patients have a high prevalence of frailty. Compared with the non-frail cohort, the frail patients tend to be male, older, and have a lower BMI with worse liver function.

KEYWORDS

cirrhosis, frailty, prevalence, systematic review, meta-analysis

Introduction

Frailty is a multidimensional clinical state of decreased physiologic reserve and increased vulnerability for patients. It is a condition in which all body systems gradually lose their capabilities, and it usually occurs in older people (1). However, as the definition of frailty evolves day by day in modern research, it has been observed in other diseases involving multiple systems, including end-stage liver diseases (2). The pathogenesis of frailty is complicated, and the possible theory describes the process as the combined influence of chronic inflammation, immune activation, and environmental and lifestyle factors (3). Currently, no agreement has been reached on the diagnosis of frailty, so various assessment instruments have been developed, such as the Edmonton Frailty Scale (EFS), Fatigue, Resistance, Ambulation, Illness, Loss of Weight (FRAIL) Index, and the Liver Frailty Index (LFI) (4, 5). The cost and prevalence of frailty are hard to evaluate due to the differences in the study population, sample size, and measurement instruments (6). Therefore, a synthesized analysis is needed to evaluate the frailty of certain diseases and to better prevent them.

Cirrhosis, on the other hand, is described as the final stage of chronic liver disease, combined with a series of complications (7). As the 11th most common cause of death (8), cirrhosis caused 1.7 million deaths worldwide in 2017, and the age-standardized death rate of cirrhosis is still rising (9). Frailty in cirrhosis patients has a great impact on mortality and life quality, especially for those awaiting transplants (10). Thus, considering the prevalence of cirrhosis and the impact of frailty, identifying the prevalence and characteristics of frailty in cirrhosis patients can be a lifesaver in end-stage liver disease management and, in the end, contribute to the primary, secondary, and tertiary prevention of liver disease.

Although previous studies have described the impact of frailty in cirrhosis patients, no unified conclusions have been reached on the estimated prevalence. Many factors, including mental health, unplanned hospital admissions, liver transplant waitlist mortality, age, and increased hospitalization days, are associated with frailty in cirrhosis patients. In addition, several high-quality observational studies that were published in recent years reported the prevalence of cirrhosis patients (11–26). Thus, we systematically gathered data from these articles to evaluate the prevalence and characteristics of frailty in cirrhosis patients.

Methods

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (27). The protocol of this meta-analysis was registered by the Prospective Register of Systematic Reviews (PROSPERO) with the following registration number: CRD42023407442.

Search strategy

We performed a thorough literature search using PubMed, Embase, Web of Science, and the Cochrane Library from inception to 29 February 2024. Key terms and the Medical Subject Headings (Mesh) terms were searched as follows: ("Liver Cirrhosis" OR "Hepatic Cirrhosis" OR "Liver Fibrosis") AND ("Frailty" OR "Frail*" OR "Frailness" OR "Debilit*"). The comprehensive search process is presented in Supplementary Table S1. All matched articles, including systematic reviews and meta-analyses, were assessed during the search.

Inclusion criteria

Studies involving the prevalence of frailty in patients with cirrhosis were included following these criteria: (1) the study is a cohort, cross-sectional, or any other observational, study; (2) patients were diagnosed with cirrhosis by medical records or clinical findings; (3) frailty was diagnosed by a standardized and validated index, such as the Liver Frailty Index (LFI) and Carolina Frailty Index (CFI), or clinical evaluations; and (4) the study population is adult (over 18 years old).

Exclusion criteria

Articles will be excluded after a comprehensive examination if they meet the following criteria: (1) the article is a study protocol, case report, conference abstract, or any other type of article that is not original; (2) the article is a duplicate; and (3) the article has irrelevant outcomes.

Study selection

The selection was performed independently by two reviewers (RX and XJ) by checking titles and abstracts to exclude irrelevant studies. The full text of selected articles will be assessed to determine whether they are eligible. A senior reviewer (MW) carried out the final assessment when there was a disagreement between authors performing the screening.

Data extraction

Following the guideline for data extraction for systematic reviews and meta-analysis, two reviewers (RX and XJ) independently worked on eligible articles, collecting the following information: author, country, year of publication, study design, the diagnosis of frailty, age, sex distribution, body mass index (BMI), and the number of cirrhosis patients with or without frailty. A discussion will be held to settle any disagreements with a third reviewer (MW).

Risk of bias assessment

To assess the quality of articles included in our meta-analysis, a modified tool (28) consisting of 10 items covering four domains of bias was used during the process. The total score of the individual observational study was from 0 to 10, and every single item was

valued at 0 or 1. The study was classified into low, moderate, and high quality with a total score of 0–5, 6–8, and 9–10.

Statistical analysis

Considering the characteristics of frailty events and total cirrhotic patients, we used a random effect model with the double-arcsine transformation to perform the meta-analysis to better calculate the estimated prevalence of frailty in patients with liver fibrosis. The chi-squared test and I^2 value were calculated to assess heterogeneity. If the P-value is < 0.1 or I^2 is $> 50\%$, then the heterogeneity would be considered high, and we would conduct a random effect model for pool analysis. Furthermore, subgroup analysis would be performed to characterize the distribution of age, sex, and BMI in such patients. The funnel plot, Egger's test, and Begg's test were combined to assess the publication bias both visually and statistically. All data in our study were analyzed by Stata/MP 14.0, and a P-value of < 0.05 was considered significant in statistical analysis.

Results

Database search and study selection

At the end of our search, 29 February 2024, a total of 1,859 studies were retrieved from the databases; among them, 371 were duplicated, and 1,488 records, including 61 meta-analyses, systematic reviews, and review articles, were excluded after viewing titles and abstracts. After assessing the full articles of the remaining 29 studies, 16 studies were considered eligible for our meta-analysis. Figure 1 shows the PRISMA flowchart describing study selection and screening.

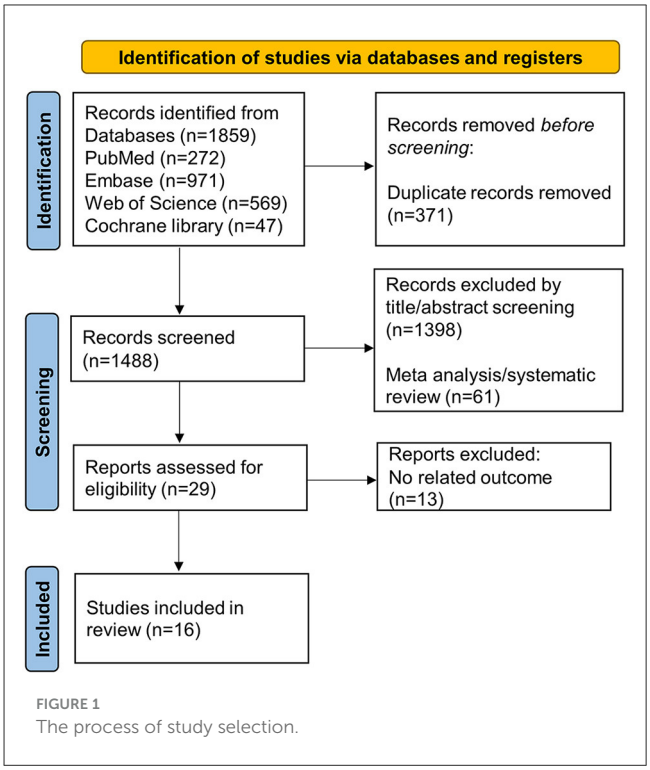

FIGURE 1
The process of study selection.

Study characteristics

In conclusion, in 16 observational studies (11–26), 8,406 cirrhosis patients were included, with sample sizes ranging from 126 to 1,623. The eligible studies, with data gathered from China, Chile, Japan, Slovakia, Spain, Thailand, and the United States, were published from 2018 to 2023. The baseline characteristics of the included articles are shown in Table 1.

Quality assessment

There were 13 cohort studies and three cross-sectional studies included in our study, and the average score of them was 8.92 and 9.00, respectively, indicating the eligible studies had high quality. Among all the included studies, 11 cohort studies (13–17, 19, 21, 22, 24–26) and two cross-sectional studies (18, 20) were rated over 9, which were classified as high-quality articles, and the remaining articles were deemed moderate quality. The detailed score is shown in Table 2.

The prevalence of frailty in cirrhosis patients

The 16 included studies (11–26), which were all observational, reported a prevalence of frailty in cirrhosis patients ranging from 9 to 65%, and the overall estimated prevalence was 27% (95% CI: 21–33%; $I^2 = 97.7\%$, $P < 0.001$). The detailed result is displayed in Figure 2. Through the process, the heterogeneity of the data was examined by sensitivity analysis to find the possible cause, and none of the individual studies reversed the pooled-effect size, as shown in Supplementary Figure S1, which suggested the high stability of our study.

Subgroup analysis

To better characterize the distribution of age, sex, and BMI in cirrhotic patients with frailty, we performed meta-analyses for subgroups separately in the frail and non-frail cohorts from five studies (19, 21–23, 25). Through the subgroup analysis, we found that the cirrhosis patients in the frail cohort tend to have a higher age, with a mean age of 63.3 (95% CI: 59.9, 66.7; $Z = 36.48$; $P < 0.001$), and a larger proportion of male patients, with a mean of 73.5% (95% CI: 71.4, 75.5%; $Z = 7.65$; $P < 0.001$). Meanwhile, the patients in the non-frail cohort are more likely to have a high BMI, with a mean of 28.4 (95% CI: 24.1, 32.7; $Z = 13.07$; $P < 0.001$). The detailed result is displayed in Table 3. Additionally, the researchers conducted meta-analyses on the frail and non-frail cohorts to discuss the distribution of the Child-Pugh class in cirrhosis patients, as shown in Table 4. Compared to the frail population, up to 53.6% (95% CI: 29.0, 78.2%; $P < 0.001$) of

TABLE 1 Baseline characteristics of the study population.

References	Year	Country	Study design	Diagnosis	Age	sample size	M/F	BMI	Frail	Non-frail
Siyu et al. (23)	2023	China	Cross-sectional study	The Liver Frailty Index	(–)	387	(–)	(–)	39	348
Mao et al. (17)	2023	China	Retrospective cohort study	Carolina Frailty Index with minor modifications	63 (57, 69)	245	111/134	24.3 (21.3, 27.3)	27	218
Cullaro et al. (13)	2022	United States	Prospective cohort study	The Liver Frailty Index	58 (50, 63)	1,033	589/444	(–)	313	720
Berry et al. (12)	2022	United States	Cohort study	The Liver Frailty Index	58 (50, 63)	1,623	949/674	28.3 (24.9, 32.6)	451	1,172
Bajaj et al. (11)	2022	United States	Prospective cohort study	The clinical frailty scale	(–)	442	(–)	(–)	40	402
Xu et al. (26)	2021	United States	Prospective cohort study	The Liver Frailty Index	(–)	1,623	(–)	(–)	451	1,172
Soto et al. (25)	2021	Chile	Prospective cohort study	Clinical evaluation	64 ± 8.3	126	62/60	29.4 ± 4.8	82	44
Skladany et al. (24)	2021	Slovakia	Cohort study	The Liver Frailty Index	(–)	385	291/94	(–)	184	201
Siramolpiwat et al. (22)	2021	Thailand	Cohort study	The Liver Frailty Index	62.5 ± 9.3	152	87/65	(–)	37	115
Serper et al. (21)	2021	United States	Prospective cohort study	The Liver Frailty Index	57 ± 12	211	115/96	30.0 ± 7.0	124	87
Roman et al. (19)	2021	Spain	Prospective cohort study	Five Fried Frailty criteria of the cardiovascular health study	(–)	135	97/38	(–)	35	100
Feng et al. (15)	2021	China	Cohort study	Carolina Frailty Index	63 (55, 68)	202	98/104	23.7 (20.5, 26.5)	35	167
Deng et al. (14)	2021	United States	Cohort study	The Liver Frailty Index	61 (54–65)	233	134/99	29 (25–33)	43	190
Saeki et al. (20)	2020	Japan	Cross-sectional study	Fried's five components	70 (59–76)	291	137/154	23.1 (20.8–26.0)	81	210
Lai et al. (16)	2020	United States	Cohort study	The Liver Frailty Index	60 (53–64)	983	649/334	28 (25–32)	151	832
Puchades et al. (18)	2018	Spain	Cross-sectional study	The Liver Frailty Index	60 (53–65)	335	221/114	28 (25–33)	53	282

non-frail patients were classified into Child-Pugh A, with a lower proportion of the patients classified into Child-Pugh B and Child-Pugh C at 39.2% (95% CI: 20.3, 58.2%; $P < 0.001$) and 12.3% (95% CI: 8.8, 15.7%; $P < 0.001$), respectively.

Publication bias

To examine whether there was a publication bias, we conducted Begg's test and Egger's test, which resulted in PBegg = 0.150 ($P > 0.05$) and PEgger = 0.200 ($P > 0.05$), indicating that no publication bias was observed in our study statistically. Visually, the symmetrical funnel plot is shown in Figure 3, which also proves the same conclusion.

Discussion

Our meta-analysis compared the outcomes of data collected from 16 observational studies regarding the prevalence of frailty in 8,406 patients with cirrhosis. An estimated prevalence of 27% was shown in cirrhosis patients with frailty. We further investigated the distribution of sex, age, and BMI in cirrhosis patients with or without frailty to characterize our target patients. As a result, the frail cohort has a higher average age, a larger proportion of male patients, and a lower BMI than the non-frail cohort. Such results can help clinicians to easily and swiftly identify frailty in patients with cirrhosis.

At the time our research is being conducted, few research studies have focused on the prevalence of frailty in cirrhosis patients. A previous meta-analysis (29) discussed the frailty

TABLE 2 Risk of bias in the included articles.

Study items	Publication year	1	2	3	4	5	6	7	8	9	10	Scores	Overall quality
Cohort studies													
Mao et al. (17)	2023	1	1	1	0	1	1	1	1	1	1	9	High
Cullaro et al. (13)	2022	1	1	1	1	1	1	1	1	0	1	9	High
Berry et al. (12)	2022	1	1	1	0	1	1	1	1	0	1	8	Moderate
Bajaj et al. (11)	2022	0	1	0	1	1	1	1	1	1	1	8	Moderate
Xu et al. (26)	2021	1	1	1	0	1	1	1	1	1	1	9	High
Soto et al. (25)	2021	1	1	1	0	1	1	1	1	1	1	9	High
Skladany et al. (24)	2021	1	1	1	1	1	1	1	0	1	1	9	High
Siramolpiwat et al. (22)	2021	1	1	1	0	1	1	1	1	1	1	9	High
Serper et al. (21)	2021	1	1	1	1	1	0	1	1	1	1	9	High
Roman et al. (19)	2021	1	1	1	1	1	1	1	1	1	1	10	High
Feng et al. (15)	2021	1	1	1	0	1	1	1	1	1	1	9	High
Lai et al. (2)	2021	1	1	1	1	1	0	1	1	1	1	9	High
Deng et al. (14)	2020	1	0	1	1	1	1	1	1	1	1	9	High
Cross-sectional studies													
Siyu et al. (23)	2023	1	1	1	1	1	0	1	1	0	1	8	Moderate
Saeki et al. (20)	2020	1	1	1	1	1	1	0	1	1	1	9	High
Puchades et al. (18)	2018	1	1	1	1	1	1	1	1	1	1	10	High

1. Was the study's target population a close representation of the national population about relevant variables? 2. Was the sampling frame a true or close representation of the target population? 3. Was some form of random selection used to select the sample, or was a census undertaken? 4. Was the likelihood of nonresponse bias minimal? 5. Were data collected directly from the subjects (as opposed to a proxy)? 6. Was an acceptable case definition used in the study? 7. Was the study instrument that measured the parameter of interest shown to have validity and reliability? 8. Was the same mode of data collection used for all subjects? 9. Was the length of the shortest prevalence period for the parameter of interest appropriate? 10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?

assessment instruments in cirrhosis patients, including the Liver Frailty Index (LFI), the Short Physical Performance Battery, the 5-m gait speed, and routine nursing assessment, but it did not research the estimated prevalence of frailty as our study does. Currently, the most frequent tool is the LFI, which is a performance-based tool comprising three separate tests, including grip strength, chair stands, and balance testing. The other most commonly used tools are the Fried phenotype and the Fried Frailty Index (FFI), which cover weight loss, exhaustion, low physical activity, slowness, and weakness. Other tools include the Karnofsky Performance Scale (KPS), which assesses patients' ability to work and care for themselves, and the short physical performance battery (SPPB), which includes a balance test, gait speed test, and chair stand test. Several other meta-analyses (30–34) calculated the prevalence of frailty in different populations, which resulted in 11% in the older community-dwelling population, 53% in long-term care residents, 5%—29% in patients with human immunodeficiency virus (HIV) infections, and 37% in patients with end-stage renal disease. All the studies mentioned above discussed a specific population without cirrhosis. Overall, our study filled the gap in the prevalence of frailty in cirrhosis patients.

There have been several reports demonstrating the association of factors with frailty in cirrhosis patients, including mental health, unplanned hospital admissions, liver transplant waitlist mortality, age, and increased hospitalization days. For instance, researchers have identified age as a significant influencing factor for frailty (35). Our findings also reveal that the cirrhosis patients in the frail cohort tend to have a higher age when compared to the non-frail cohort. However, it should be noted that a recent report found that cirrhosis patients may also experience frailty at a younger age (23). Together with our findings, aged cirrhosis patients require more frequent evaluation in clinics.

In the current study, a male predominance of frailty among cirrhosis was found, which is against the published findings (19, 25). First, these studies and a few others included a lot more male than female patients, which may create bias. Second, male patients with cirrhosis are more likely to have comorbidities such as spontaneous bacterial peritonitis and hepatocellular carcinoma, which may also accelerate frailty.

With our findings, we hope cirrhosis patients can be identified swiftly and easily during outpatient visits and inpatient admissions to improve the quality of life and mortality in end-stage liver disease patients. Considering the prevalence of frailty in cirrhosis patients, all kinds of assessment instruments should be used regarding local demographics in hepatology clinical practice. After the diagnosis of frailty, a comprehensive intervention combining in-hospital treatment with community-based physical activity and nutritional programs (36) should be taken to reduce the prevalence and

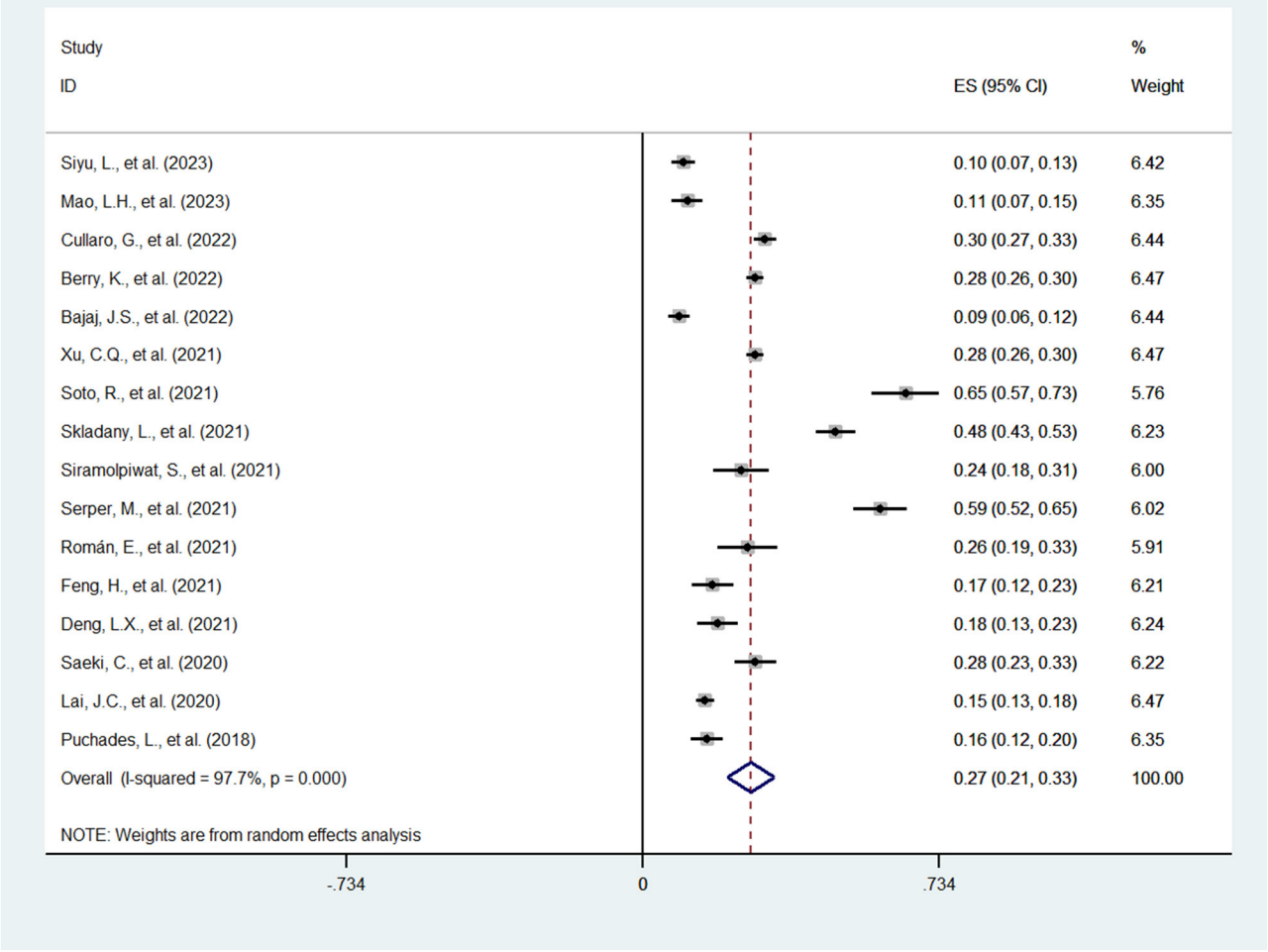

FIGURE 2
Meta-analysis of the prevalence of frailty in cirrhosis patients.

TABLE 3 Subgroup analysis of the distribution of age, sex, and BMI in frail and non-frail cirrhosis patients.

	Frail	Non-frail
Age (years)	63.3 (95% CI: 59.9, 66.7; $Z = 36.48$; $P < 0.001$)	59.5 (95% CI: 54.7, 64.3; $Z = 24.38$; $P < 0.001$)
BMI	28.1 (95% CI: 26.0, 30.1; $Z = 26.95$; $P < 0.001$)	28.4 (95% CI: 24.1, 32.7; $Z = 13.07$; $P < 0.001$)
Male (%)	73.5% (95% CI: 71.4, 75.5%; $Z = 7.65$; $P < 0.001$)	54.7% (95% CI: 52.2, 57.1%; $Z = 20.52$, $P < 0.001$)

TABLE 4 Subgroup analysis of the proportion of different Child-Pugh classes in frail and non-frail cirrhosis patients.

	Frail	Non-frail
A	30.0% (95% CI: 10.7, 49.3%; $P < 0.001$)	53.6% (95% CI: 29.0, 78.2%; $P < 0.001$)
B	54.8% (95% CI: 43.1, 66.5%; $P < 0.001$)	39.2% (95% CI: 20.3, 58.2%; $P < 0.001$)
C	23.4% (95% CI: 13.2, 33.7%; $P < 0.001$)	12.3% (95% CI: 8.8, 15.7%; $P < 0.001$)

improve mortality in end-stage liver disease patients, especially those on the liver transplant waitlist.

To better summarize our meta-analysis, we are focusing on the prevalence of frailty in cirrhosis patients and calculating related parameters through subgroup analysis. The result of the sensitivity analysis and assessing the risk of bias in prevalence studies through the modified tool (28) indicated the credibility and stability of our study. There are also limitations in our meta-analysis. First, the study population in articles meeting the inclusion criteria comes from a diverse background, including age, nationality, race, etc., which can cause bias. Second, during the research, high heterogeneity was found. As limited data was retrieved, the cause of heterogeneity was unable to be identified. Third, we failed to acquire sufficient data regarding the complications, etiology, and other factors that might be influencing the prevalence of frailty

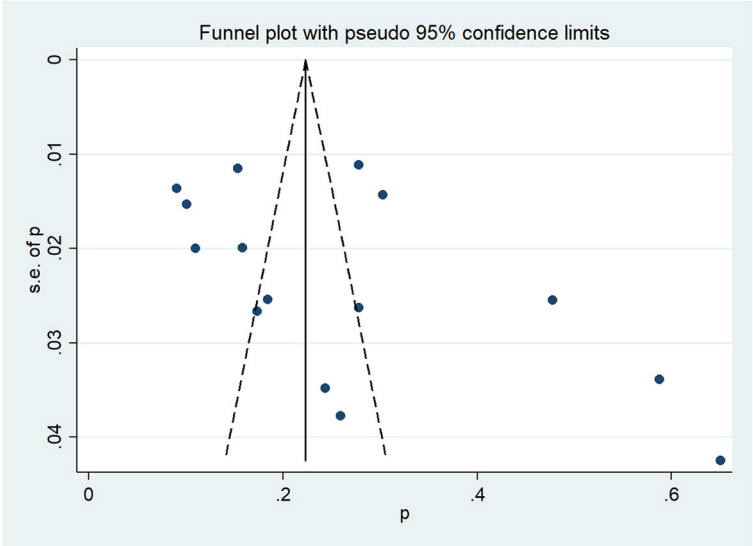

FIGURE 3
The funnel plot of the prevalence of frailty in cirrhosis patients.

in cirrhosis patients. Fourth, the data on the clinical impact of frailty, such as the severity of liver cirrhosis, in the reported papers chosen is limited. Future work could explore the clinical impact for the benefit of clinical practice. Finally, funnel plot asymmetry cannot discriminate between publication bias and other sources of asymmetry, and meta-regression could be employed to assess the heterogeneity.

Conclusion

This meta-analysis indicated that the estimated prevalence of frailty in cirrhosis patients stayed at a high level, and compared to the non-frail cohort, the frail patients tend to be male, older, and have a lower BMI with worse liver function. With these findings, we hope more resources and efforts can be directed toward reducing the prevalence of frailty in cirrhosis patients and improving their mortality. This approach could potentially lead to better health outcomes and quality of life for these patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

RX: Data curation, Validation, Writing – original draft, Writing – review & editing. XJ: Data curation, Validation, Writing – original draft, Writing – review & editing. CY: Data curation, Funding acquisition, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1353406/full#supplementary-material

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The predictive value of γ-glutamyl transferase to serum albumin ratio in hepatocellular carcinoma patients after liver transplantation

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Background: Elevated preoperative γ-glutamyl transferase (GGT) levels or reduced serum albumin levels have been established as negative prognostic factors for patients with hepatocellular carcinoma (HCC) and various other tumors. Nonetheless, the prognostic significance of the GGT to serum albumin ratio (GAR) in liver transplantation (LT) therapy for HCC is still not well-defined.

Methods: A retrospective analysis was conducted on the clinical data of 141 HCC patients who underwent LT at Shulan (Hangzhou) Hospital from June 2017 to November 2020. Using the receiver operating characteristic (ROC) curve, the optimal GAR cutoff value to predict outcomes following LT was assessed. Univariate and multivariate Cox proportional hazards regression analyses were used to identify independent risk factors associated with both overall survival (OS) and recurrence-free survival (RFS).

Results: A GAR value of 2.04 was identified as the optimal cutoff for predicting both OS and RFS, with a sensitivity of 63.2% and a specificity of 74.8%. Among these patients, 80 (56.7%) and 90 (63.8%) met the Milan and the University of California San Francisco (UCSF) criteria, respectively. Univariate Cox regression analysis showed that microvascular invasion (MVI), maximum tumor size (>5 cm), total tumor size (>8 cm), liver cirrhosis, TNM stage (III), and GAR (≥2.04) were significantly associated with both postoperative OS and RFS in patients with HCC (all $p < 0.05$). Multivariate Cox regression analysis indicated that GAR (≥2.04) was independently linked with RFS and OS.

Conclusion: Pre-transplant GAR ≥2.04 is an independent correlate of prognosis and survival outcomes after LT for HCC and can be used as a prognostic indicator for both mortality and tumor recurrence following LT.

KEYWORDS

liver transplantation, hepatocellular carcinoma, gamma-glutamyl transferase to serum albumin ratio, overall survival, prognosis

Introduction

Hepatocellular carcinoma (HCC) is a malignancy that significantly affects human health, ranking as one of the most prevalent malignancies globally and the third highest cause of cancer-related deaths (1, 2). Chronic liver disease and cirrhosis cause approximately 2 million deaths worldwide each year. Although there are various strategies and methods currently available for treating HCC and end-stage liver disease, liver transplantation (LT) remains one of the most effective treatments. Indications include irreversible liver damage (i.e., cirrhosis) caused by chronic viral infections, excessive alcohol consumption, and liver cancer or acute liver failure (1, 3). In 1996, the Milan criteria were introduced as guidelines for LT in HCC patients, although they were later considered too strict. Subsequently, a research team from the University of California, San Francisco (UCSF), and Hangzhou, China, proposed more comprehensive standards, including the Hangzhou standard, which incorporated innovative elements such as preoperative serum alpha-fetoprotein (AFP) levels and tumor histological differentiation (4–7). However, it is now understood that for HCC patients undergoing LT, their prognosis is influenced by multiple factors, including graft function, rejection, recurrence, and complications. Statistics indicate a 5-year survival rate of 75–80% following surgery, with a relatively low risk of recurrence at approximately 15% (1). Therefore, it is crucial to identify reliable biomarkers or test indicators to assess the prognosis of patients with HCC.

In recent years, inflammation scores, such as the neutrophil-to-lymphocyte ratio (NLR) (8) and platelet-to-lymphocyte ratio (PLR) (9), have demonstrated the ability to reflect the body's immunological function and inflammatory status. These indicators not only provide insights into the likelihood of recurrence and early mortality after LT for HCC but are also directly associated with patient survival post-transplantation. Additionally, studies based on preoperative γ-glutamyl transferase (GGT) to serum albumin ratio (GAR) have shown a strong correlation with the prognosis after partial resection of HCC and radical surgery for pancreatic ductal adenocarcinoma (10–12). However, there is limited research on the prognostic significance of GAR in HCC patients undergoing LT, which led to the current study to evaluate its importance.

Method

Patients

This retrospective study included 306 consecutive patients diagnosed with HCC between June 2017 and November 2020 at the Hepatobiliary and Pancreatic Surgery Department of Shulan (Hangzhou) Hospital, Affiliated with Zhejiang Shuren University Shulan International Medical College, China. All patients underwent LT, with subsequent pathological confirmation of HCC. Inclusion criteria were: (1) pathological HCC diagnosis after the first orthotopic LT, (2) absence of other tumors or metastases, and (3) adherence to the Hangzhou criteria. Patients were excluded if they had, (1) other tumors or metastases ($n = 63$), (2) exceeded the Hangzhou criteria ($n = 84$), (3) were younger than 18 years old ($n = 2$), (4) died within three months after LT ($n = 10$), or (5) lacked sufficient blood records and clinical data ($n = 6$) (Figure 1A). Ultimately, 141 patients were enrolled in this study.

Data collection methods

Electronic medical records were used to collect clinical information from enrolled patients. The primary data consisted of age, gender, tumor size, hepatitis virus infection, tumor number,

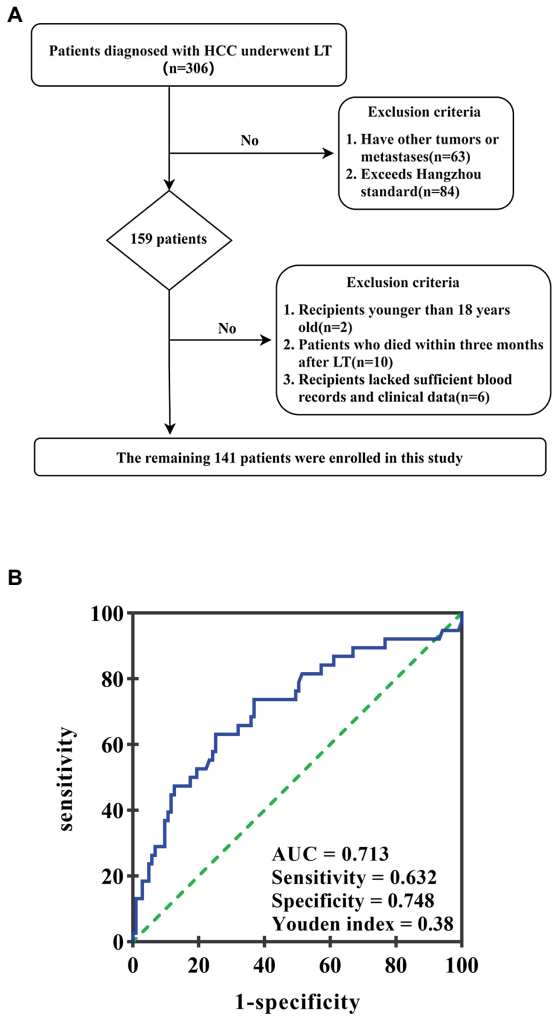

FIGURE 1
(A) The patient selection flowchart. **(B)** ROC curve of the GAR value in predicting HCC recurrence after liver transplantation. The area under the ROC curve is 0.713. GAR value 2.04 is considered the best cutoff value; its highest Youden index is 0.38; sensitivity and specificity are 63.2 and 74.8%, respectively.

Abbreviations: HCC, Hepatocellular carcinoma; LT, Liver transplantation; GAR, γ-glutamyl transferase to serum albumin ratio; NLR, Neutrophil-to-lymphocyte ratio; ALR, Aspartate aminotransferase-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; ROC, Receiver operating characteristic; AAPR, Albumin/alkaline phosphatase ratio; ALBI, Albumin-bilirubin grading system; GLR, γ-glutamyl transferase to lymphocyte ratio; OS, Overall survival; RFS, Recurrence-free survival; NLR, Neutrophil-to-lymphocyte ratio.

preoperative serum albumin, differentiation, and GGT. The GGT-to-serum albumin ratio was calculated by dividing preoperative gamma-glutamyl transpeptidase by albumin. To determine the best cutoff value of preoperative GAR for predicting post-transplantation long-term survival, ROC analysis and the Youden index were used. When the area under the receiver operating characteristic (ROC) curve was 0.713, the Youden index achieved its highest value, resulting in a sensitivity of 63.2% and a specificity of 74.8%. Consequently, a GAR of 2.04 was identified as the optimal critical value (Figure 1).

Follow-up

All transplant recipients were followed closely on an outpatient basis. The average follow-up duration was 46.6 months, ranging from 9.6 to 75.3 months. During the first 6 months after surgery, physical examinations and laboratory tests were performed monthly for each patient. This frequency decreased to every 3–6 months for the next 2 years and biannually thereafter. Contrast-enhanced abdominal computed tomography (CT) or magnetic resonance imaging (MRI) scans were performed routinely every 6 months. If local recurrence or distant metastasis was suspected, specific imaging examinations, including CT, MRI, bone scans, and positron emission tomography-computed tomography (PET-CT), were conducted promptly. Overall survival (OS) was defined as the time between LT and either death or the last follow-up. Recurrence-free survival (RFS) was defined as the time from LT to tumor recurrence or the last follow-up.

Statistical analysis

Two clinicians independently completed the follow-up and data review. Categorical variables were presented as numbers and percentages. They were compared using either Pearson's chi-square analysis or Fisher's exact test, depending on which was more appropriate. For continuous variables, Student's t-test was used for normally distributed data, while the Mann–Whitney rank sum test was used for non-normally distributed data. ROC curve analysis was used to determine the optimal GAR cutoff value for predicting post-transplantation survival and recurrence of HCC patients. The cutoff value corresponding to the highest Youden index was considered optimal. Kaplan–Meier estimation and log-rank tests were used to compare OS and disease-free survival between recipients in the high and low GAR ratio groups. Univariate and multivariate analyses were conducted using the Cox proportional hazards model to identify significant prognostic factors. All statistical tests were two-sided, with a significance level set at a p-value of <0.05. Data analysis was performed using SPSS software (Version 27.0, Chicago, IL, United States) and GraphPad Prism (Version 8.0, San Diego, CA, United States).

Results

Patient baseline clinical characteristics

The 141 eligible HCC patients were categorized into high-risk (GAR ≥2.04, $n = 50$) and low-risk (GAR <2.04, $n = 91$) groups based on the optimal cutoff value. Table 1 summarizes the baseline characteristics of all enrolled patients. Among the patients, 92.2% ($n = 130$) were male and 7.8% ($n = 11$) were female. A total of 57 patients had microvascular invasion (MVI). According to the AJCC Version 8 TNM staging system (13), 30 patients were classified into stage I + II and 111 into stage III. The Barcelona Clinic Liver Cancer (BCLC) system (14) categorized 84 patients as 0 + A and 57 as B + D. Additionally, 44.7% ($n = 63$) of patients were over the median age of 55, 34% ($n = 48$) had a BMI greater than 25, and 83.7% ($n = 118$) had a total tumor size of ≤8 cm. Approximately half (49.6%, $n = 70$) of the patients had ascites before surgery, 95.7% ($n = 135$) of the patients had liver cirrhosis, and 80.1% ($n = 113$) were positive for hepatitis B preoperatively. Significant differences in tumor-related characteristics were observed between the GAR groups, including tumor number, total tumor diameter, and compliance with the Milan, UCSF, or Hangzhou criteria ($p < 0.05$). Interestingly, GAR was not significantly associated with MELD score (>20) ($p = 0.291$), as well as histopathological characteristics such as tumor differentiation ($p = 0.162$), liver cirrhosis ($p > 0.999$), and maximum tumor diameter (>5 cm) ($p = 0.093$).

Prognostic significance of GAR on short- and long-term outcomes

The prognostic significance of GAR for short- and long-term outcomes was assessed. Among HCC patients meeting the Hangzhou criteria ($n = 141$), 56.7% ($n = 80$) met the Milan criteria, and 63.8% ($n = 90$) met the UCSF criteria. The median follow-up duration for all patients was 48 months (range: 9.6–75.3 months), during which 41 patients (38%) were confirmed to have died, and 47 patients (43.5%) had confirmed recurrences. The median OS stood at 48 months, accompanied by 1-, 3-, and 5-year OS rates of 95.7, 77.3, and 70.6%, respectively. Concurrently, the median RFS time was 44.58 months, with RFS rates at 1, 3, and 5 years recorded as 80.9, 72.9, and 70.9%, respectively.

The Kaplan–Meier survival curves indicated that the low GAR group exhibited significantly higher 1-, 3-, and 5-year OS rates in contrast to the high GAR group (98.9, 85.7, and 84.4% vs. 92.0, 62.0, and 51.4%, respectively; $p < 0.001$, Figure 2A). Similarly, at 1-, 3-, and 5-year post-surgery, the low GAR group demonstrated significantly elevated RFS rates compared to the high GAR group (89.0, 84.5, and 82.9% vs. 66.0, 51.9, and 49.3%, respectively; $p < 0.001$, Figure 2B).

Patients were categorized based on whether they met or exceeded the Milan and UCSF criteria. Interestingly, the results showed that within both criteria groups, patients with a GAR of 2.04 or higher (high GAR) had a significantly poorer prognosis (Figures 3, 4). However, when looking specifically at patients who met the Milan or UCSF criteria (within criteria), there were no significant differences in OS or RFS between the high GAR and low GAR groups ($p > 0.05$; Figures 3A,C, 4A,C). In contrast, for patients who exceeded the Milan or UCSF criteria (beyond criteria, specifically standard or UCSF standard group), a high GAR was significantly associated with worse OS and RFS, highlighting its impact on the prognosis of HCC patients after transplantation ($p < 0.05$; Figures 3B,D, 4B,D).

Following the outcomes of univariate analysis, maximum tumor size (>5 cm) [hazard ratio (HR): 3.143; 95% confidence interval (CI): 1.556–6.349; $p = 0.001$], total tumor size (>8 cm) (HR: 3.580; 95% CI: 1.824–7.028; $p < 0.001$), MVI (Yes) (HR: 3.349; 95% CI: 1.712–6.551;

TABLE 1 Comparison of clinical characteristics between GAR ≥ 2.04 and GAR < 2.04 groups.

Variables	All patients (n = 141)	GAR grade		p-value
		Low (n = 91)	High (n = 50)	
Gender (Male/Female)	130/11	82/9	48/2	0.328
Age, years (>55/≤55)	63/78	38/53	25/25	0.346
BMI, kg/m^2 (>25/≤25)	48/93	35/56	13/37	0.135
Smoking (Yes/No)	61/80	38/53	23/27	0.627
Alcohol (Yes/No)	54/87	34/57	20/30	0.758
MVI (Yes/No)	57/84	31/60	26/24	**0.038**
Tumor number (Multiple/Single)	78/63	43/48	35/15	**0.009**
Maximum tumor size, cm (>5/≤5)	19/122	9/82	10/40	0.093
Total tumor size, cm (>8/≤8)	23/118	9/82	14/36	**0.005**
TNM stages (III/I-II)	30/111	17/74	13/37	0.310
BCLC stages(B+D/0+A)	57/84	41/50	16/34	0.153
AFP, ng/mL (>400/≤400)	18/123	10/81	8/42	0.394
Liver cirrhosis (Yes/No)	135/6	87/4	48/2	>0.999
MELD score (>20/≤20)	20/121	15/76	5/45	0.291
Differentiation (Moderate/Well)	103/38	70/21	33/17	0.162
Positive HBsAg (+/−)	113/28	72/19	41/9	0.682
Ascites (+/−)	70/71	47/44	23/27	0.521
Milan criteria (Yes/No)	80/61	64/27	16/34	**<0.001**
UCSF criteria (Yes/No)	90/51	70/21	20/30	**<0.001**
Hangzhou criteria (A/B)	118/23	82/9	36/14	**0.005**

Bold values are $p < 0.05$.

$p < 0.001$), TNM stage (III) (HR: 2.522; 95% CI: 1.303–4.802; $p = 0.006$), and GAR (≥2.04) (HR: 3.685; 95% CI: 1.903–7.133; $p < 0.001$) demonstrated significant associations with OS (Table 2). To minimize the potential interactions among these variables, significant variables in the univariate Cox regression analysis were identified and incorporated into the multivariate Cox proportional hazards model. Following the multivariate analysis, MVI(Yes) (HR: 2.452; 95% CI: 1.210–4.969; $p = 0.013$), and pre-LT serological test ratios, only GAR appeared as an independent risk factor for OS (HR: 2.744; 95% CI: 1.369–5.496; $p = 0.004$) (Table 2; Figure 5A).

Similarly, we performed a multivariate Cox analysis aimed at identifying prognostic factors for RFS (Table 3). We found that liver cirrhosis (Yes) (HR = 9.895; 95% CI: 3.198–30.611; $p < 0.001$) and GAR (HR = 3.357; 95% CI: 1.648–6.840; $p < 0.001$) were associated with a higher risk of RFS (Table 3; Figure 5B).

Our comprehensive analysis results demonstrate that high GAR values in preoperative non-invasive serum tests (HR: 2.744, $p = 0.004$ for OS; HR: 3.357, $p < 0.001$ for RFS) function as independent prognostic factors for adverse OS and RFS, as illustrated in Figure 5.

We conducted a deeper investigation into the relationship between the serum albumin/alkaline phosphatase ratio (AAPR), the albumin–bilirubin (ALBI) grading system, the γ-glutamyl transferase to lymphocyte count ratio (GLR), and the aminotransferase-to-lymphocyte ratio (ALR). These parameters have previously been examined in patients who have undergone liver transplantation or those who have undergone resection for HCC (15–18), NLR, PLR, and ALBI with clinicopathological features and their ability to predict survival outcomes using the same methods described above (10). ROC curve analysis was used to compare the accuracy of these markers in predicting the prognosis of patients with HCC who met the Hangzhou criteria for LT. The Youden index calculations determined the optimal cutoff points: −2.26 for ALBI grade, 0.58 for AAPR, 69.47 for PLR, 86.97 for GLR, 145.01 for ALR, and 2.59 for NLR. The AUCs of OS for ALBI, AAPR, PLR, NLR, ALR, and GLR were 0.552, 0.603, 0.613, 0.551, 0.538, and 0.620, respectively (Figure 6A). The AUCs of RFS for ALBI, AAPR, PLR, NLR, ALR, and GLR were 0.577, 0.565, 0.671, 0.591, 0.528, and 0.614, respectively (Figure 6B).

Discussion

HCC incidence and mortality rates vary significantly worldwide due to factors such as genetics, environment, lifestyle, and infections. LT remains a crucial treatment for HCC patients (1). Predicting the prognosis for patients with HCC is essential. While a biopsy is the standard for diagnosing HCC and MVI, it also carries risks such as bleeding and needle tract tumor spread. In contrast, serum tumor markers such as AFP offer a non-invasive and reproducible approach

TABLE 2 Univariate and multivariate cox analyses show prognostic factors for OS.

Variables	Univariate analysis			Multivariate analysis		
	HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value
Gender (Male/Female)	1.713	0.412–7.123	0.459			
Age, years (>55/≤55)	1.169	0.614–2.227	0.634			
BMI, kg/m^2 (>25/≤25)	1.534	0.745–3.159	0.246			
Smoking (Yes/No)	1.052	0.553–2.004	0.877			
Alcohol (Yes/No)	1.253	0.658–2.385	0.493			
MVI (Yes/No)	3.349	1.712–6.551	**<0.001**	2.452	1.210–4.969	**0.013**
Tumor number (Multiple/Single)	1.447	0.748–2.800	0.272			
Maximum tumor size, cm (>5/≤5)	3.143	1.556–6.349	**0.001**	1.417	0.595–3.375	0.431
Total tumor size, cm (>8/≤8)	3.580	1.824–7.028	**<0.001**	1.876	0.759–4.638	0.173
AFP, ng/mL (>400/≤400)	1.308	0.546–3.130	0.547			
Liver cirrhosis (Yes/No)	3.581	1.263–10.152	**0.016**	2.418	0.798–7.327	0.118
MELD score (>20/≤20)	1.156	0.451–2.963	0.763			
Differentiation (Moderate/Well)	1.441	0.660–3.146	0.359			
TNM stage (III/I+II)	2.522	1.303–4.802	**0.006**	1.157	0.497–2.692	0.735
BCLC stage (B+D/0+A)	1.517	0.775–2.968	0.223			
Positive HBsAg (+/−)	1.404	0.587–3.359	0.446			
Ascites (+/−)	1.197	0.631–2.269	0.582			
NLR grade (≥2.59/<2.59)	1.334	0.682–2.607	0.400			
PLR grade (≥69.47/<69.47)	2.187	0.963–4.969	0.062			
AAPR grade (≥0.58/<0.58)	1.057	0.442–2.528	0.902			
ALBI grade [≥(−2.26)/<(−2.26)]	1.135	0.599–2.152	0.698			
GLR grade (≥86.97/<86.97)	1.355	0.711–2.580	0.356			
ALR grade (≥145.01/<145.01)	1.785	0.885–3.599	0.105			
GAR grade (≥2.04/<2.04)	3.685	1.903–7.133	**<0.001**	2.744	1.369–5.496	**0.004**

Bold values are $p < 0.05$.

TABLE 3 Univariate and multivariate cox analyses show prognostic factors for RFS.

Variables	Univariate analysis			Multivariate analysis		
value	HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value
Gender (Male/Female)	1.679	0.405–6.960	0.440			
Age, years (>55/≤55)	1.150	0.614–2.153	0.663			
BMI, kg/m^2 (>25/≤25)	1.890	0.900–3.971	0.093			
Smoking (Yes/No)	1.149	0.610–2.164	0.667			
Alcohol (Yes/No)	1.410	0.756–2.630	0.280			
MVI (Yes/No)	2.993	1.577–5.680	**<0.001**	1.569	0.784–3.137	0.203
Tumor number (Multiple/Single)	2.471	1.234–4.948	**0.011**	1.743	0.824–3.687	0.146
Maximum tumor size, cm (>5/≤5)	2.836	1.384–5.812	**0.004**	1.335	0.539–3.308	0.533
Total tumor size, cm (>8/≤8)	4.494	2.359–8.561	**<0.001**	2.076	0.843–5.113	0.112
AFP, ng/mL (>400/≤400)	1.312	0.551–3.126	0.540			
Liver cirrhosis (Yes/No)	7.473	2.887–19.343	**<0.001**	9.895	3.198–30.611	**<0.001**
MELD score (>20/≤20)	1.005	0.422–2.395	0.990			
Differentiation (Moderate/Well)	1.297	0.617–2.725	0.492			
TNM stage (III/I+II)	2.801	1.475–5.318	**0.002**	1.271	0.530–3.049	0.591
BCLC stage (B+D/0+A)	1.572	0.811–3.049	0.181			

(Continued)

TABLE 3 (Continued)

Variables	Univariate analysis			Multivariate analysis		
value	HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value
Positive HBsAg (+/−)	1.501	0.630–3.574	0.359			
Ascites (+/−)	1.121	0.602–2.085	0.719			
NLR grade (≥2.59/<2.59)	1.567	0.808–3.037	0.184			
PLR grade (≥69.47/<69.47)	3.912	1.532–9.989	**0.004**	2.443	0.929–6.421	0.070
AAPR grade (≥0.58/<0.58)	1.831	0.891–3.748	0.098			
AIBI grade [≥(−2.26)/< (−2.26)]	1.413	0.760–2.628	0.275			
GLR grade (≥86.97/<86.97)	1.043	0.545–1.998	0.899			
ALR grade (≥145.01/<145.01)	1.694	0.848–3.391	0.137			
GAR grade (≥2.04/<2.04)	3.859	2.032–7.328	**<0.001**	3.357	1.648–6.840	**<0.001**

Bold values are $p < 0.05$.

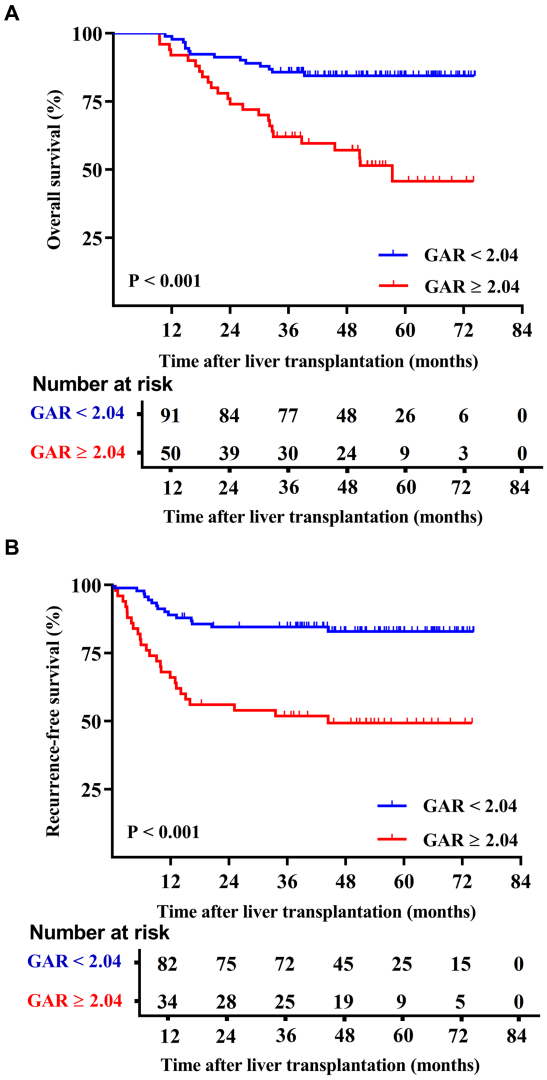

FIGURE 2
Comparison of overall patient survival and recurrence-free survival between GAR ≥ 2.04 and <2.04 patients. The patients were divided into two groups according to the pre-transplant GAR cutoff value of 2.04. Recipients in the GAR < 2.04 group presented significantly higher OS rates [$p < 0.001$ **(A)**] and RFS rates [$p < 0.001$ **(B)**] than those in the GAR ≥ 2.04 group.

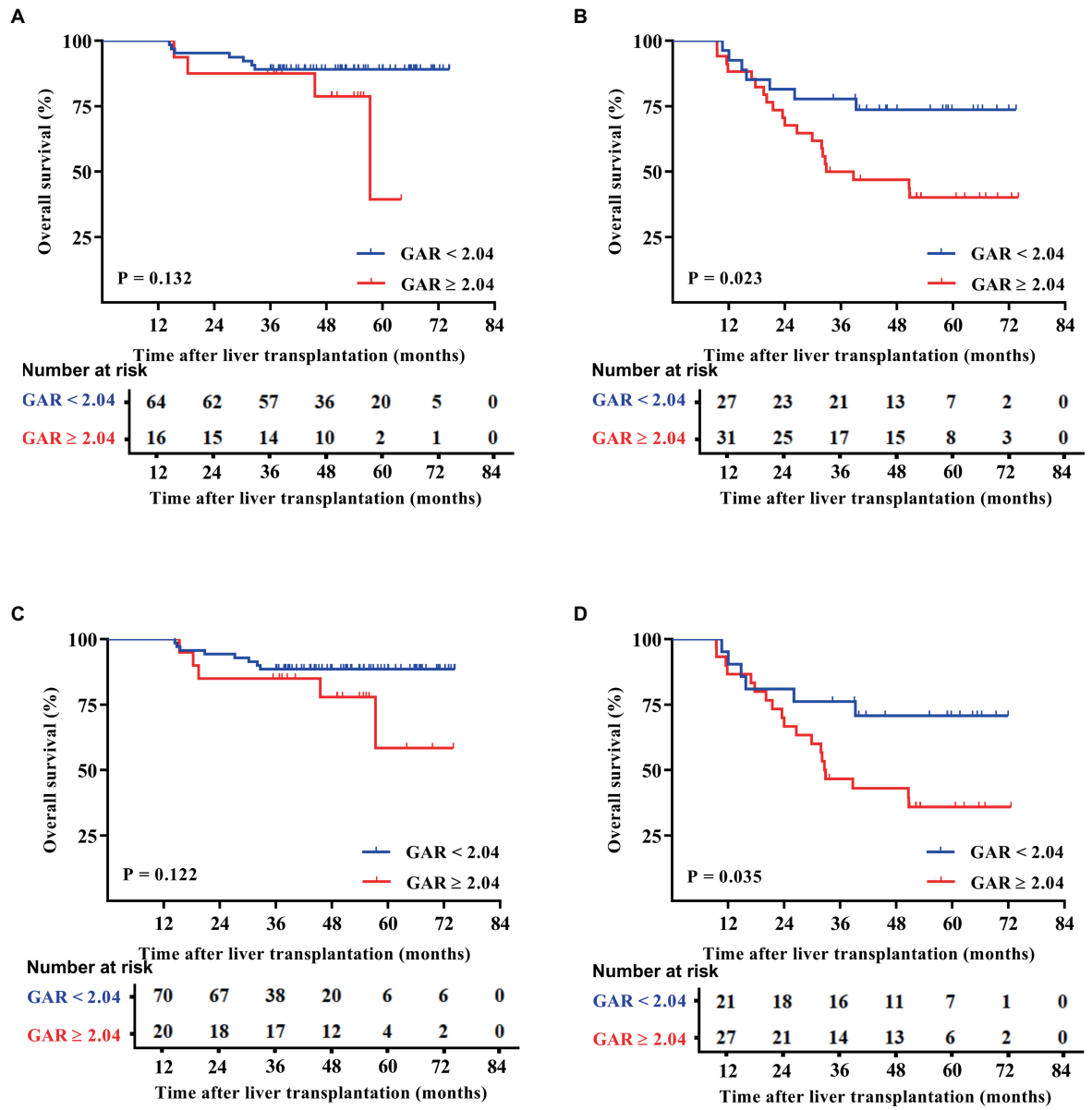

FIGURE 3
OS outcomes of patients were divided according to the Milan and UCSF criteria. The patients were divided into the Milan **(A)** and UCSF **(C)** criteria, beyond Milan **(B)** and UCSF **(D)** criteria. The OS of the Milan, UCSF, and GAR < 2.04 groups was comparable with that of the GAR ≥ 2.04 group, and no statistically significant difference was presented [$p > 0.05$ **(A,C)**]. Patients in the beyond Milan and UCSF criteria and GAR < 2.04 groups had significantly higher OS than the GAR ≥ 2.04 group [$p < 0.05$ **(B,D)**].

for early diagnosis (1). Our data demonstrated that the GAR score, which involves serum GGT and serum protein levels, is a simple and convenient ratio with significant predictive value. Previous studies have shown the importance of these serum markers in tumor progression (14, 15).

GGT plays a crucial role in glutathione metabolism. It not only protects cells from oxidative damage but also contributes to oxidative stress, impacting proliferation, apoptosis, and immune responses. The activity of GGT primarily reflects the extent of harm to liver and bile duct cells (19, 20), which is associated not only with HCC but also with the digestive system, respiratory tract, breast, and lymphoma, affecting the risk of cancer in these systems (21–23). In the context of HCC treatment, such as liver resection and LT, an increase in GGT is considered an indicator of a poor prognosis (24–26). Similarly, serum albumin, reflecting liver health and nutritional status, serves as a potent free radical scavenger, antioxidant, and immune regulator, in addition to its role in transporting substances and maintaining blood vessel pressure. It interacts with various substances, including metal ions, toxic metabolites, and inflammatory mediators, thereby influencing the body's inflammatory and antioxidant responses (27–29), and various pathological conditions such as malnutrition, weakened immune defenses, and reduced cell function are closely

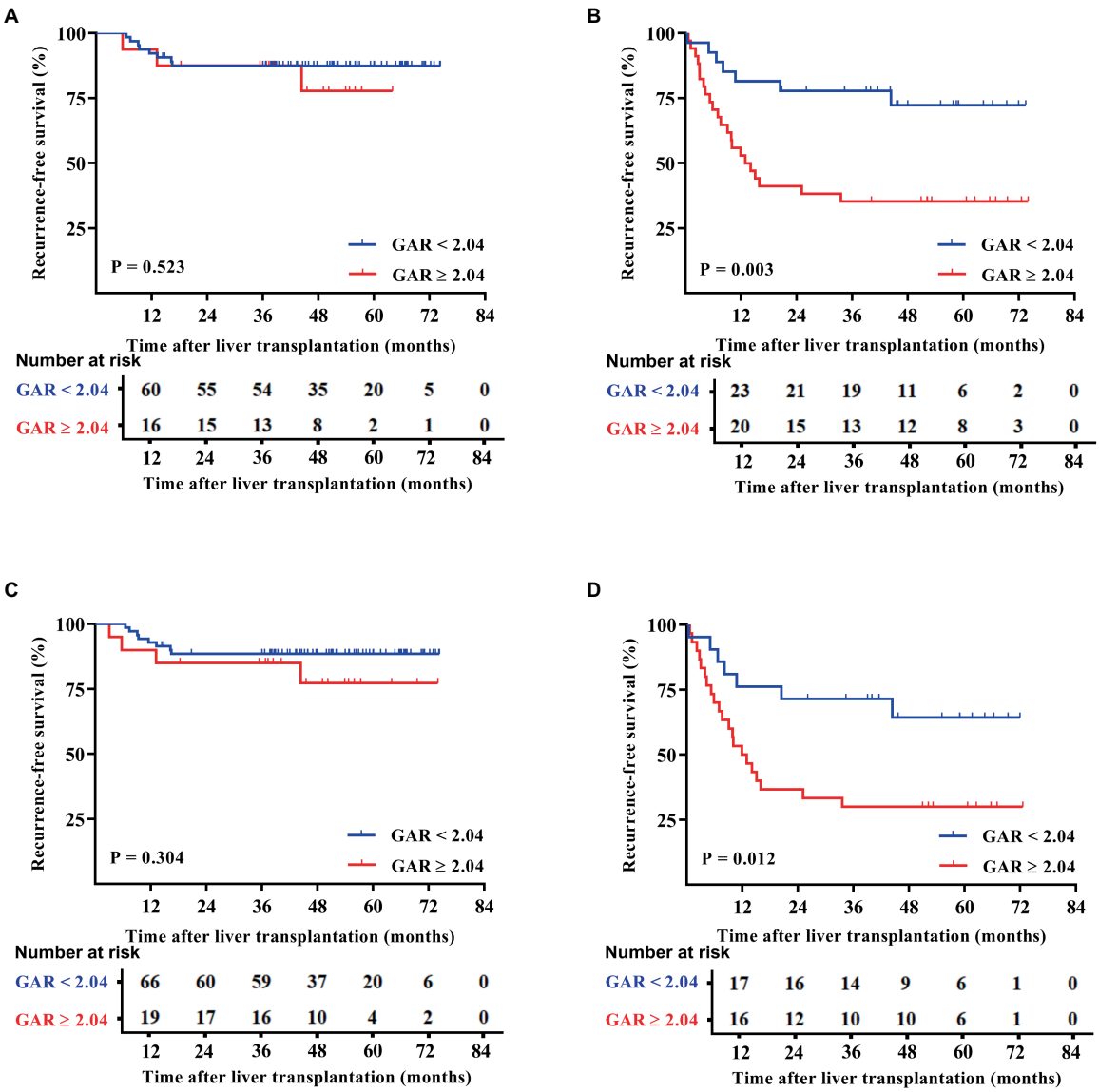

FIGURE 4
RFS outcomes of patients were divided according to the Milan and UCSF criteria. The patients were divided into the Milan **(A)** and UCSF **(C)** criteria, beyond Milan **(B)**, and UCSF **(D)** criteria. The RFS of the Milan or UCSF and GAR < 2.04 groups was comparable with that of the GAR≥2.04 group, and no statistically significant difference was presented [$p > 0.05$ **(A,C)**]. Patients in the beyond Milan and UCSF criteria and GAR < 2.04 groups had significantly higher RFS than the GAR ≥ 2.04 group [$p < 0.05$ **(B,D)**].

interconnected with these factors (29, 30). Furthermore, the latest Meld 3.0 version incorporates serum albumin into its calculations to enhance mortality prediction accuracy (31).

Current evidence suggests that GGT and serum albumin play a vital role in assessing liver function, nutritional status, and inflammatory response. Their value in predicting prognoses, particularly for cancer, is undeniable. Tumor-associated inflammation, often induced by innate immune cells, can promote tumor growth while suppressing adaptive immune responses—a key area of cancer research and drug development. Oncogenic mutations and signaling alterations in cancer cells can further exacerbate this inflammation by affecting chemokines, cytokines, tissue structure, oxygen pressure, and microbial translocation (32). In the context of basic research, some researchers have combined these two indicators and demonstrated that the GAR holds significant predictive value in assessing the prognosis of numerous hepatobiliary disease-related disorders. For instance, GAR can predict liver fibrosis and cirrhosis in patients with chronic hepatitis B (33), and it is strongly associated with the prognosis of liver resection in cirrhosis and HCC cases (12, 34). Post-surgery, high GAR values often correlate with reduced OS and RFS (10, 35). Moreover, GAR has shown predictive value for independent prognosis in patients undergoing pancreatic ductal adenocarcinoma surgery (11). Nonetheless, its predictive potential in LT surgery research warrants further exploration, given that it has not been extensively investigated. When combined with our findings from this research, it was found that GAR could identify high-risk HCC transplant patients. Prior to LT for

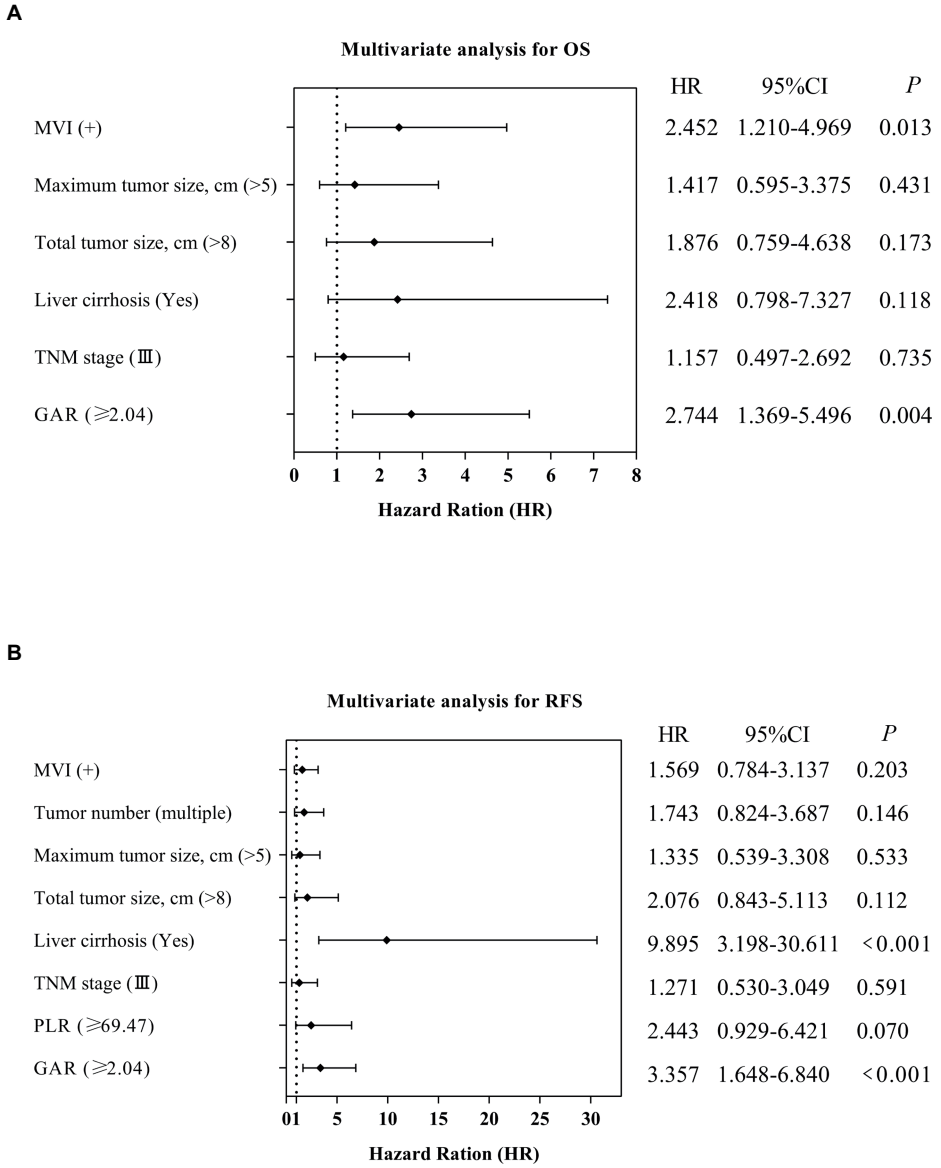

FIGURE 5
Forest plot comparing independent risk factors affecting OS and RFS after transplantation in HCC patients according to multivariate analysis.

cirrhosis or HCC, effective serological screening and selection can reduce the risk of post-transplant HCC recurrence, thereby improving the quality of life for patients and increasing their survival rates. These findings further underscore the importance of GAR in pre-transplant evaluation. However, the specific mechanism is unclear and requires further investigation.

Upon retrospective data analysis, this study revealed that patients with low GAR ratios following HCC transplantation based on Hangzhou standards exhibited better outcomes in terms of survival and tumor-free survival compared to those with high GAR ratios. High GAR values may suggest a weakened tumor resistance mechanism, potentially leading to poorer treatment outcomes for patients. While the reasons behind the increased risk of tumor recurrence and death following LT with higher GAR values remain unclear, they may shed light on previously established biological functions. Despite the numerous scoring systems and prognostic models suggested previously, such as NLR (8), PLR (9), AAPR (15), ALBI, and the systemic inflammatory response index (SIRI) (16, 36). GLR and ALR have been studied in liver transplant patients or HCC after resection patients (17, 18). These scoring systems or models hold the potential for assessing pre-surgery liver function and inflammation in LT patients. Nevertheless, their clinical applicability and accuracy currently lack standardization and remain to be validated and improved in terms of prognostic evaluation.

Our study has several limitations. First, it is a retrospective, single-center study conducted domestically with a limited sample size. Second, there may be variations in surgical techniques and

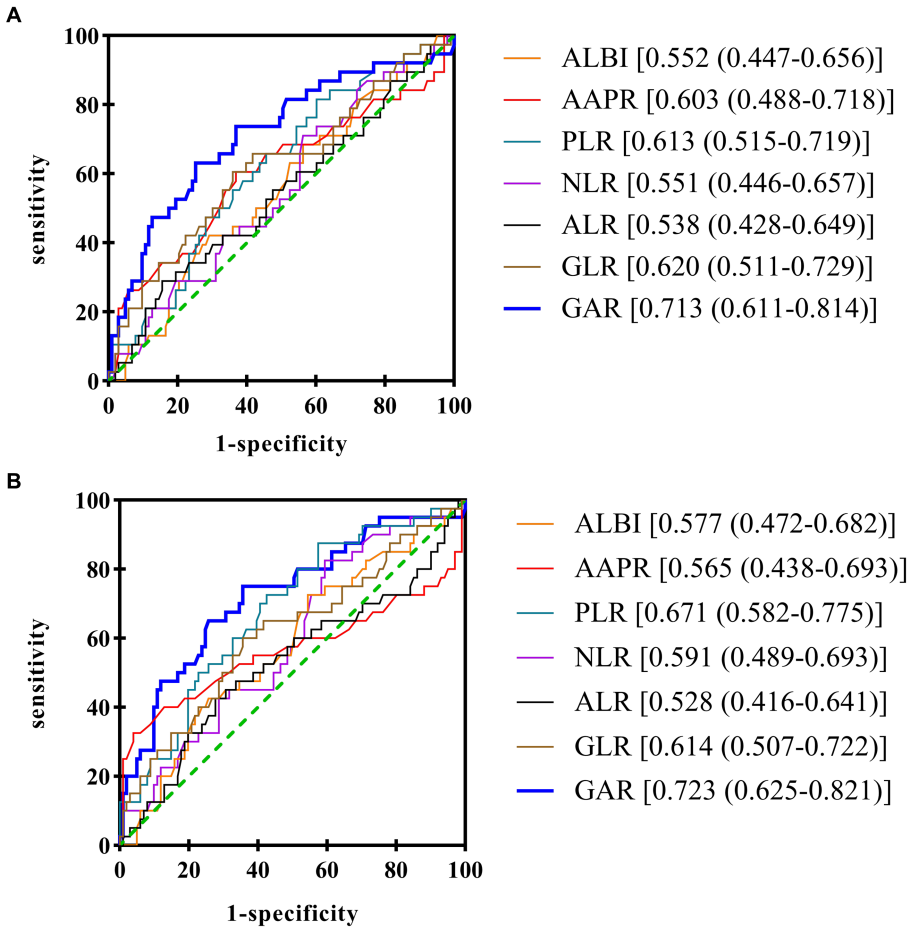

FIGURE 6
Comparison of the predictive accuracy of GAR and other variables in the derivation cohort **(A)** OS, overall survival **(B)** RFS, recurrence-free survival.

perioperative management among transplant patients. Third, the study evaluated the prognostic value of GAR only in HCC patients who underwent LT and did not assess its potential role in patients receiving downstage therapy. Finally, the lack of external validation for our findings raises the possibility of selection bias. To address these limitations and strengthen our conclusions, future investigations should be large-scale, multicenter, prospective studies with diverse patient populations.

Conclusion

This study investigated the potential of the pre-LT GGT-to-serum albumin ratio as a prognostic marker for HCC patients undergoing LT who meet the Hangzhou criteria. Our findings suggest that a pre-transplant GAR of 2.04 or higher is an independent predictor of prognosis and survival outcomes after LT for HCC. GAR is a simple and cost-effective laboratory test with the advantages of being non-invasive and reproducible. For patients who satisfy the Hangzhou criteria, the preoperative GAR offers additional prognostic data relevant to liver transplant outcomes. Moreover, a GAR value lower than 2.04 may be indicative of increased suitability for LT.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the Human Research Ethics Committee of Shulan (Hangzhou) Hospital (No: KY2024020), and complies with the principles of the Declaration of Helsinki of the World Medical Association.

Author contributions

X-YL: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation. K-WC: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Validation. NY: Data curation, Methodology, Writing – original draft, Writing – review & editing. C-HG: Data curation,

Methodology, Writing – original draft, Writing – review & editing. Q-BZ: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. J-PL: Conceptualization, Data curation, Software, Supervision, Writing – original draft, Writing – review & editing. XZ: Formal analysis, Investigation, Supervision, Validation, Writing – original draft. S-SZ: Funding acquisition, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. ZY: Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of 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.

Publisher's note

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A Mendelian randomization study on the causal effects of cigarette smoking on liver fibrosis and cirrhosis

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Background: Liver fibrosis significantly impacts public health globally. Untreated liver fibrosis eventually results in cirrhosis. Cigarette smoking is the main etiologic factor for various diseases. However, the causal effects of cigarette smoking on liver fibrosis and cirrhosis have yet to be fully elucidated.

Methods: In this study, Mendelian randomization (MR) analysis was performed to assess the association between cigarette smoking, liver fibrosis, and cirrhosis. Single-nucleotide polymorphisms (SNPs) were selected as instrumental variables from a genome-wide association study (GWAS) of European ancestry. Patients were divided into six exposure categories as follows: "ever smoked," "pack years of smoking," "age of smoking initiation," "smoking status: never," "smoking status: current," and "smoking status: previous." The outcomes of this study included liver fibrosis and cirrhosis. MR-Egger, weighted median, inverse variance weighted, simple mode, and weighted mode were selected as the analysis methods. Cochran's Q and the MR-PRESSO tests were conducted to measure heterogeneity. The MR-Egger method was performed to evaluate horizontal pleiotropy, while the "leave-one-out" analysis was performed for sensitivity testing.

Results: The results of this study showed that having a smoking history increases the risk of liver fibrosis and cirrhosis ["ever smoked": odds ratio (OR)=5.704, 95% CI: 1.166–27.910, p=0.032; "smoking status: previous": OR=99.783, 95% CI: 2.969–3.353e+03, p=0.010]. A negative correlation was observed between patients who never smoked and liver fibrosis and cirrhosis ("smoking status: never": OR=0.171, 95% CI: 0.041–0.719, p=0.016). However, there were no significant associations between "smoking status: current," "pack years of smoking," and "age of smoking initiation" and liver fibrosis and cirrhosis. Cigarette smoking did not have a significant horizontal pleiotropic effect on liver fibrosis and cirrhosis. The "Leave-one-out" sensitivity analysis indicated that the results were stable.

Conclusion: The study confirmed the causal effects of cigarette smoking on liver fibrosis and cirrhosis.

KEYWORDS

cigarette smoking, liver fibrosis, cirrhosis, Mendelian randomization, causality

Introduction

Liver disease is a long-standing challenge to global health (1). The etiological factors for chronic liver inflammation include viral hepatitis infections, alcohol consumption, drugs, metabolic factors, and autoimmune hepatitis. Untreated chronic liver inflammation causes liver fibrosis. Advanced liver fibrosis results in cirrhosis and hepatocellular carcinoma (HCC). Liver cirrhosis is the 11th most frequent cause of death worldwide, with two million deaths every year, due to complications such as chronic portal hypertension, bleeding events, and hepatic encephalopathy (2, 3).

Cigarette smoking is associated with an unhealthy lifestyle. The number of smokers is rapidly increasing, and more than one billion people worldwide have a pernicious smoking habit (4). Cigarette smoke contains more than 4,000 toxic substances that are etiological factors for various diseases (5–8). Cigarette smoking is primarily associated with respiratory diseases, and it is a major risk factor for cardiovascular diseases (9–12). Additionally, cigarette smoking increases the risk of gastrointestinal disorders (13). Cigarette smoking is associated with an increased incidence of tumors, including liver cancer (14). In addition, the incidence of liver cancer in current smokers is 1.5 times higher than that in non-smokers (15, 16). However, the effect of cigarette smoking on liver fibrosis and cirrhosis remains unclear.

Mendelian randomization (MR) is a novel tool that uses summary statistics from genome-wide association studies (GWAS) to investigate the causality between risk factors and diseases (17, 18). In MR studies, genetic variations are used as instrumental variables (IVs) (19, 20). Randomized controlled trials (RCTs) are widely accepted as the gold standard for assessing the association between exposures and outcomes. However, RCTs have many limitations, including high costs and difficulties in implementation (21, 22). MR is an analog method for RCTs (23). Additionally, MR can overcome the deficiencies of RCTs through the use of single-nucleotide polymorphisms (SNPs) as IVs (18, 24, 25). MR studies can assess the causal effects of various exposures of interest, including biological markers, daily behaviors, and disease exposures, on a range of diseases (26–28).

Previous studies estimated the causal effects of cigarette smoking on many diseases, such as stroke and cancer, using MR (7, 29–31). However, studies using MR to assess the effect of cigarette smoking on liver fibrosis and cirrhosis are limited. Hence, this MR study aimed to clarify the causal effect of cigarette smoking on liver fibrosis and cirrhosis.

Materials and methods

Data sources

A two-sample MR analysis was used to explore the association between exposure and outcome in two different samples. Compared to a one-sample MR, the sample size in a two-sample MR is larger and more precise (32). This study aimed to analyze the causal effects of cigarette smoking on liver fibrosis and cirrhosis. As such, six exposures related to cigarette smoking were selected, including "ever smoked," "pack years of smoking," "age of smoking initiation," "non-smokers," "current smokers," and "former smokers." The "ever smoked" group included participants who ever had smoking habits, regardless of whether they were currently smoking or not. Pack years of smoking were calculated based on the age of starting smoking and the age of quitting smoking, or the duration from starting smoking to participating in this program of the Integrative Epidemiology Unit GWAS database. The "non-smokers" group included participants who had never smoked. The "current smokers" group consists of participants who had the smoking habit and currently still smoke. The "former smokers" group consists of participants who used to smoke before but had completely quit smoking recently. Compared to non-smokers, anyone who has a smoking habit before or currently is considered to have a smoking history.

The exposed genetic variants were obtained from the Integrative Epidemiology Unit GWAS database. The sample sizes for "ever smoked," "pack years of smoking," "age of smoking initiation," "smoking status: never," "smoking status: current," and "smoking status: previous" were 461,066, 142,387, 341,427, 359,706, 336,024, and 336,024, respectively. The study focused on outcomes such as liver fibrosis and cirrhosis, and the genetic variants obtained from the FinnGen consortium data (1,602 cases and 332,951 controls) were also included in this study. To avoid population stratification, the genetic variants used in this analysis were derived from European ancestries. The details of the data sources are listed in Table 1. In this MR study, genetic variants strongly correlated with exposure but failed to show associations with confounders. Therefore, genetic variants did not have an impact on the outcome, except through exposure (33).

SNP selection

SNPs with a p-value less than 5×10^{-8} and minor frequency > 1% as IVs, relating to "ever smoked," "pack years," "age of smoking initiation," "non-smokers," "current smokers," and "former smokers," were selected. Furthermore, the clumping method ($r^2 < 0.001$, clumping distance = 10,000 kb) was used to avoid linkage disequilibrium. The F-statistic was used to evaluate the strength of the association between IVs and exposure. The general threshold of F in an MR study was 10 (31). SNPs with an F less than 10 were considered weak instruments and were eliminated from further MR analyses (32). In this study, F was calculated as β^2/SE^2 (β stands for the effect on the risk of exposure, and SE stands for the standard error) (34–36).

Statistical analysis

MR-Egger, weighted median, inverse variance weighted (IVW), simple mode, and weighted mode were selected as the methods of analysis. IVW is considered the most reliable method in MR analyses, and it was performed to assess the heterogeneity among the IVs (37). Cochran's Q and the MR-PRESSO tests were used to measure the heterogeneity of individual SNPs (38). Heterogeneity existed if the p-value was less than 0.05 and the random-effects model was implemented; otherwise, the fixed-effects model was used. Funnel plots were used to show heterogeneity by drawing Wald ratios for the SNPs. The MR-Egger method was used to evaluate horizontal pleiotropy; if the intercept was significantly different from 0, with a p-value less than 0.05, horizontal pleiotropic effects existed (39). Finally, sensitivity analyses were conducted using the "leave-one-out" analysis.

TABLE 1 Detailed information of datasets included for MR analysis.

Exposure	Consortium			Sample size	Population	Sex	Number of SNPs
Ever smoked	MRC-IEU			461,066	European	Males and Females	9,851,867
Pack years of smoking	MRC-IEU			142,387	European	Males and Females	9,851,867
Age of smoking initiation	GWAS and Sequencing Consortium of Alcohol and Nicotine use			341,427	European	Males and Females	11,894,779
Smoking status: never	Neale lab			359,706	European	Males and Females	13,586,591
Smoking status: current	Neale Lab			336,024	European	Males and Females	10,894,596
Smoking status: previous	Neale Lab			336,024	European	Males and Females	10,894,596
Outcomes	**Consortium**	**Cases**	**Control**	**Sample size**	**Population**	**Sex**	**Number of SNPs**
Liver fibrosis and cirrhosis	FinnGen	1,602	332,951	334,553	European	Males and Females	20,169,350

In this study, the statistically significant level was set at $p < 0.05$. All analyses were performed in R (version 4.2.2) with the "TwoSampleMR" package (version 0.5.6).

Results

The SNPs chosen for this MR analysis are presented in Supplementary File. In the final MR analysis, a total of 67 SNPs were related to "ever smoked," 5 SNPs were related to "pack years of smoking," 9 SNPs were related to "age of smoking initiation," 61 SNPs were related to "smoking status: never," 15 SNPs were related to "smoking status: current," and 18 SNPs were related to "smoking status: previous." The F statistics for these SNPs were more than 10, with mean *F* values of 40.63, 37.62, 81.23, 41.77, 40.79, and 35.30 for "ever smoked," "pack years of smoking," "age of smoking initiation," "smoking status: never," "smoking status: current," and "smoking status: previous," respectively. Furthermore, a weak instrumental variable bias was non-existent.

In this MR study, five methods were used to assess the causal effects of cigarette smoking on liver fibrosis and cirrhosis in the European population, and the IVW method was considered the most reliable method. As presented in Table 2, having a smoking history was correlated with liver fibrosis and cirrhosis ("ever smoked," IVW: OR = 5.704, 95% CI: 1.166–27.910, $p = 0.032$). "Smoking status: previous" also had positive associations with liver fibrosis and cirrhosis (IVW: OR = 99.783, 95% CI: 2.969 – 3.353e + 03, $p = 0.010$). "Smoking status: never" had negative associations with liver fibrosis and cirrhosis (IVW: OR = 0.171, 95% CI: 0.04–0.719, $p = 0.016$). Additionally, "smoking status: current," "pack years of smoking," and "age of smoking initiation" were not associated with liver fibrosis and cirrhosis. The effect of each SNP on liver fibrosis and cirrhosis is shown in Figures 1, 2.

The results of the MR-Egger test indicated the absence of pleiotropy (p ˃0.05). In addition, all SNPs in this MR analysis did not affect liver fibrosis and cirrhosis via biological pathways independently (Table 3). Heterogeneity was tested using Cochran's Q test and the MR-PRESSO test; the results are presented in Table 3. Funnel plots were used to visualize the heterogeneity of the effects of SNPs on liver fibrosis and cirrhosis; the results are presented in Supplementary Figure 1. The results of the leave-one-out analysis revealed reliable associations between exposures and outcomes (Figure 3).

Discussion

This is the first study to assess the causality of cigarette smoking on liver fibrosis and cirrhosis using the MR analysis and GWAS. In this study, five MR analysis methods were implemented. The results indicated that a smoking history increases the risk of liver fibrosis and cirrhosis, while a lack of a smoking history reduces this risk.

Liver fibrosis is a common liver disease that results in cirrhosis with the progression of fibrosis (40). The activation of hepatic stellate cells (HSCs) is a key etiological factor in liver fibrosis (41–43). Currently, liver fibrosis is assumed to be the result of pathological changes caused by an imbalance between extracellular matrix synthesis and degradation. In addition, liver tissues injured by viruses, alcohol, and other hazardous factors activate HSCs that secrete excessive extracellular matrix (ECM). The accumulation of ECM destroys the physiological architecture of the liver and leads to regression of fibrosis (44, 45).

Cigarette smoking is established as a harmful determinant of health that endangers almost all organ systems. However, the impact of cigarette smoking on the liver has been poorly studied. In recent years, the effect of cigarette smoking on the liver has attracted increasing attention (46). Long-term exposure to cigarette smoke increases the secretion of proinflammatory cytokines involved in liver cell injury (47). In addition, cigarette smoking is closely associated with non-alcoholic liver disease (NAFLD) (48). The cross-sectional study has found that increasing the daily cigarette quantity correlates with an increased incidence of fatty liver (49). A recent MR analysis identified that cigarette smoking is causally implicated in NAFLD (50). Cigarette smoking significantly increases the risk of liver fibrosis in NAFLD patients (51). Furthermore, second-hand smoking induces liver inflammation through the deregulation of genes and molecular pathways that regulate lipid metabolism (52).

This study aimed to establish a correlation between cigarette smoking and liver fibrosis and cirrhosis. To assess the causal effects, we selected six exposures, including "ever smoked," "pack years of smoking," "age of smoking initiation," "smoking status: never," "smoking status: current," and "smoking status: previous." Through strict statistical analysis, a positive correlation was identified between cigarette smoking and liver fibrosis and cirrhosis. "Ever smoked" and "smoking status: previous" were risk factors, whereas "smoking status: never" was seemingly protective. These results provide evidence supporting the adverse effects of cigarette smoking on liver fibrosis and cirrhosis. Cigarette smoke contains reactive

TABLE 2 MR analysis from each method assessing the causal effects of smoking on liver fibrosis and cirrhosis.

Outcome	Exposure	Method	OR(95%CI)	*p*-value
Fibrosis and cirrhosis of the liver	Ever smoked	MR Egger	1.160(0.001–2406.793)	0.970
		Weighted median	14.097(1.754–113.327)	0.013
		Inverse variance weighted	5.704(1.166–27.910)	0.032
		Simple mode	76.732(0.261–22556.380)	0.139
		Weighted mode	43.153(0.406–4587.957)	0.118
Fibrosis and cirrhosis of the liver	Pack years of smoking	MR Egger	0.895(0.161–4.970)	0.902
		Weighted median	0.544(0.217–1.359)	0.202
		Inverse variance weighted	0.608(0.286–1.294)	0.197
		Simple mode	0.647(0.143–2.935)	0.580
		Weighted mode	0.567(0.222–1.447)	0.297
Fibrosis and cirrhosis of the liver	Age of Smoking Initiation	MR Egger	1.134(0.009–138.311)	0.962
		Weighted median	1.298(0.136–12.370)	0.820
		Inverse variance weighted	1.396(0.225–8.665)	0.720
		Simple mode	3.407(0.159–72.768)	0.477
		Weighted mode	0.621(0.031–12.399)	0.770
Fibrosis and cirrhosis of the liver	Smoking status: never	MR Egger	21.316(0.056–8130.904)	0.317
		Weighted median	0.104(0.016–0.663)	0.017
		Inverse variance weighted	0.171 (0.041–0.719)	0.016
		Simple mode	0.021(0.000–1.898)	0.098
		Weighted mode	0.030(0.001–1.297)	0.073
Fibrosis and cirrhosis of the liver	Smoking status: current	MR Egger	0.038(1.752e-13-8.243e+09)	0.810
		Weighted median	0.469(1.654e-03-1.328e+02)	0.792
		Inverse variance weighted	1.366(1.879e-02-9.934e+01)	0.887
		Simple mode	1.014(2.569e-05-4.006e+04)	0.998
		Weighted mode	0.269(1.304e-05-5.545e+03)	0.799
Fibrosis and cirrhosis of the liver	Smoking status: previous	MR Egger	4.889(5.494e-12-4.351e+12)	0.911
		Weighted median	168.202(5.980–4.730e+03)	0.003
		Inverse variance weighted	99.783(2.969–3.353e+03)	0.010
		Simple mode	210.954(0.491–9.057e+04)	0.102
		Weighted mode	171.430(0.380–7.731e+04)	0.117

oxygen species (ROS). Substantial evidence has demonstrated that ROS causes systemic oxidative damage to membrane lipids, proteins, and DNA in the human body. An imbalance between ROS and endogenous antioxidant defenses leads to oxidative stress (53–55). Several studies have shown that oxidative stress plays an important role in the development of liver fibrosis and cirrhosis (56–58). Cigarette smoking causes gut microbiota dysbiosis, which is closely associated with various diseases, including liver fibrosis (48). In this MR study, "ever smoked," "smoking status: previous," and "smoking status: never" rather than "smoking status: current," "pack years of smoking," or "age of smoking initiation" were found to be associated with liver fibrosis and cirrhosis. We speculate that it is related to the mechanisms mentioned above. This may be understood as the long-term effect of smoking on liver fibrosis and cirrhosis once it begins, and it will not stop due to changes in smoking status.

"Smoking status: previous" had positive associations with liver fibrosis and cirrhosis. The participants in the "Smoking status: previous" group had successfully quit smoking. The results indicated that smoking cessation could not reduce the risk of fibrosis and cirrhosis caused by smoking. This is an expected result because the smoking group included previous smokers who may had weight gain after smoking cessation. Both current smoking and weight gain after smoking cessation lead to a higher risk of NAFLD, which is a major cause of liver fibrosis and cirrhosis (59, 60).

The greatest advantage of this study is the use of a two-sample MR as a statistical method. Using a two-sample MR eliminates the bias caused by confounding and reverse causality issues (32). In addition, the population in this study was restricted to Europe; therefore, the bias resulting from population stratification was reduced. The exposures and outcomes were derived from different GWAS consortiums, and there was no sample overlap. Furthermore,

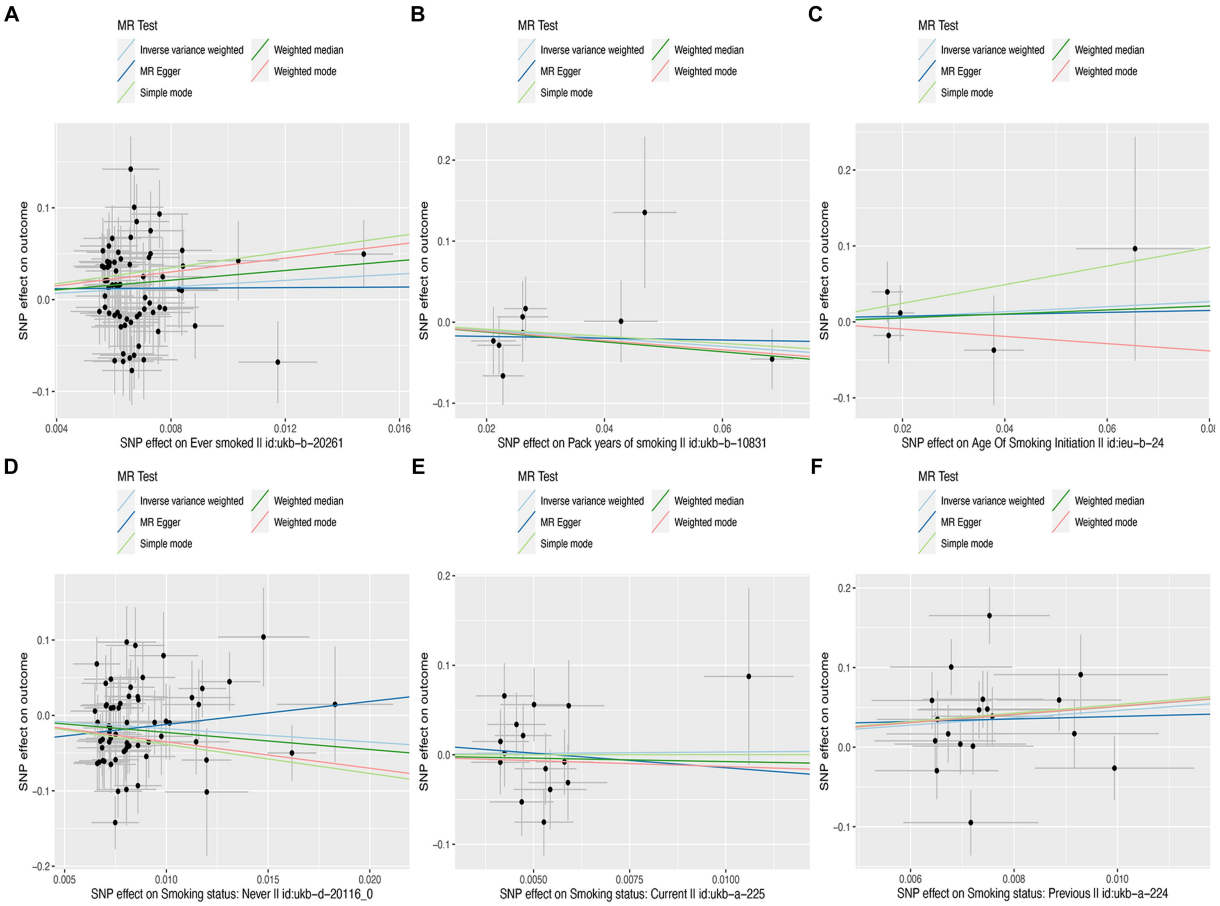

FIGURE 1
Scatter plots of effects of cigarette smoking-associated SNPs on liver fibrosis and cirrhosis. **(A)** "Ever smoked"; **(B)** "Pack years of smoking"; **(C)** "Age of smoking initiation"; **(D)** "Smoking status: never"; **(E)** "Smoking status: current"; and **(F)** "Smoking status: previous."

the sample size in this study was sufficiently large to ensure the reliability of the results. Finally, five MR methods were used, and several sensitivity analyses were conducted to ensure the stability of the results.

However, limitations were present in this study. First, only the European population was assessed; therefore, the findings might not apply to other races. Second, the exposures focused on cigarette smoking habits and status, but the cigarette smoking propensity of patients was unavailable. Third, the causal effects of cigarette smoking on liver fibrosis and cirrhosis were assessed in this study, but the mechanisms underlying these effects are unknown. Fourth, cigarette filter types were not classified. Nowadays, many people have the habit of using electronic cigarettes, but this study could not observe the effects of electronic cigarettes on liver fibrosis and cirrhosis. Finally, numerous unhealthy lifestyle habits, such as drinking alcohol, lack of exercise, and unhealthy diet, are related to liver fibrosis and cirrhosis. However, the participants in this program of the Integrative Epidemiology Unit GWAS database were not grouped based on whether they had these bad habits or not, which led to our study only being able to observe the effects of smoking on liver fibrosis and cirrhosis and being unable to explore the mutual effects of these bad habits and smoking on liver fibrosis and cirrhosis. Future studies should strive to address these gaps.

Conclusion

This MR study provides evidence supporting the causal effects of cigarette smoking on liver fibrosis and cirrhosis. Cigarette smoking is a harmful determinant of health, and strict avoidance of cigarette smoking reduces the incidence of liver fibrosis and cirrhosis.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Author contributions

LG: Writing – original draft, Formal analysis, Investigation, Validation. YA: Validation, Writing – review & editing. XH: Data curation, Formal analysis, Writing – review & editing. WL: Data curation, Formal analysis, Writing – review & editing. FC: Investigation, Writing – review & editing. YF: Writing – review & editing. SG: Writing – review & editing.

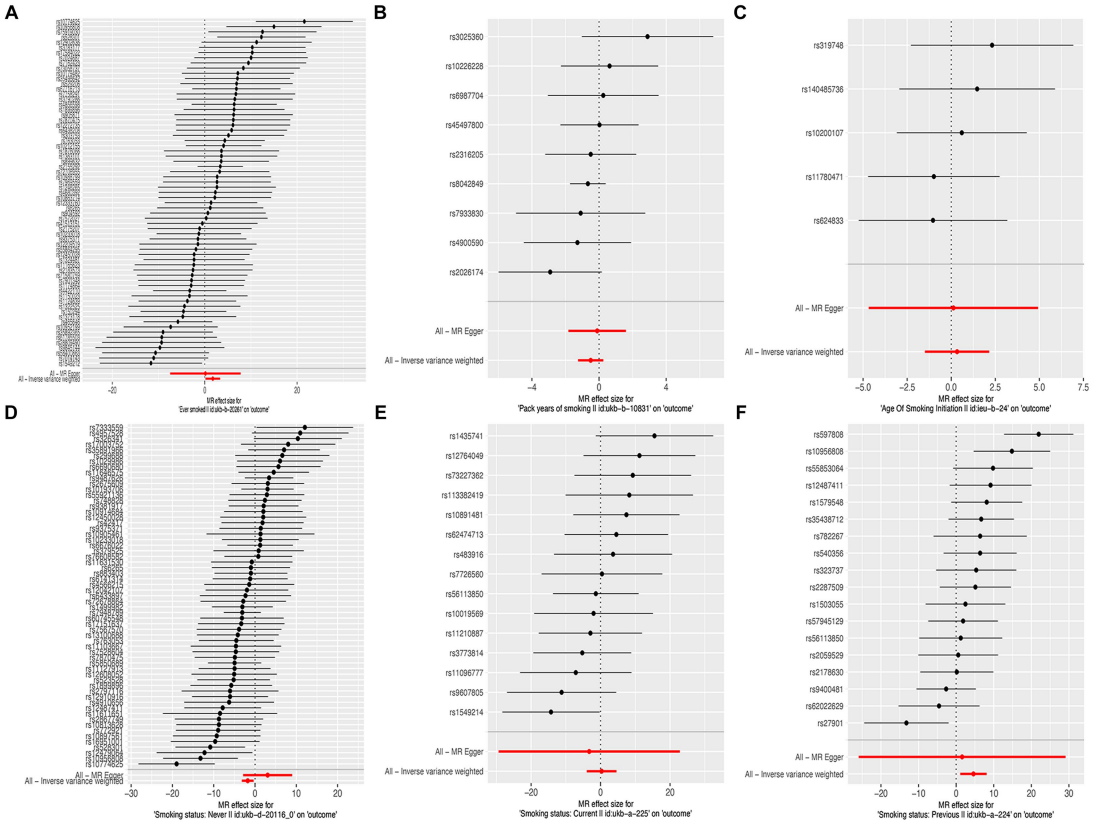

FIGURE 2
Forest plots of the effect size for each SNP for cigarette smoking on the risk of liver fibrosis and cirrhosis. **(A)** "Ever smoked"; **(B)** "Pack years of smoking"; **(C)** "Age of smoking initiation"; **(D)** "Smoking status: never"; **(E)** "Smoking status: current"; and **(F)** "Smoking status: previous."

TABLE 3 Pleiotropy and heterogeneity testing of smoking associated with liver fibrosis and cirrhosis risk using the MR Egger method.

Exposure	Method	Intercept	Standard error	*p*-value
Ever smoked	MR Egger	0.011	0.027	0.677
Pack years of smoking	MR Egger	−0.015	0.0315	0.638
Age of Smoking initiation	MR Egger	0.005	0.055	0.933
Smoking status: never	MR Egger	−0.043	0.026	0.107
Smoking status: current	MR Egger	0.018	0.067	0.789
Smoking status: previous	MR Egger	0.023	0.105	0.831

Exposure	**Method**	**Cochran's Q test**			**MR-PRESSO test**
		Q	**df**	***p*-value**	**Global Test *p*-value**
Ever smoked	Inverse variance weighted	95.466	66	0.010	0.011
	MR Egger	95.210	65	0.008	
Pack years of smoking	Inverse variance weighted	6.634	8	0.577	0.661
	MR Egger	6.392	7	0.495	
Age of Smoking Initiation	Inverse variance weighted	1.870	4	0.760	0.779
	MR Egger	1.861	3	0.602	
Smoking status: never	Inverse variance weighted	89.178	60	0.009	0.0094
	MR Egger	85.298	59	0.014	
Smoking status: current	Inverse variance weighted	15.941	14	0.317	0.327
	MR Egger	15.850	13	0.257	
Smoking status: previous	Inverse variance weighted	37.988	17	0.002	0.004
	MR Egger	37.877	16	0.002	

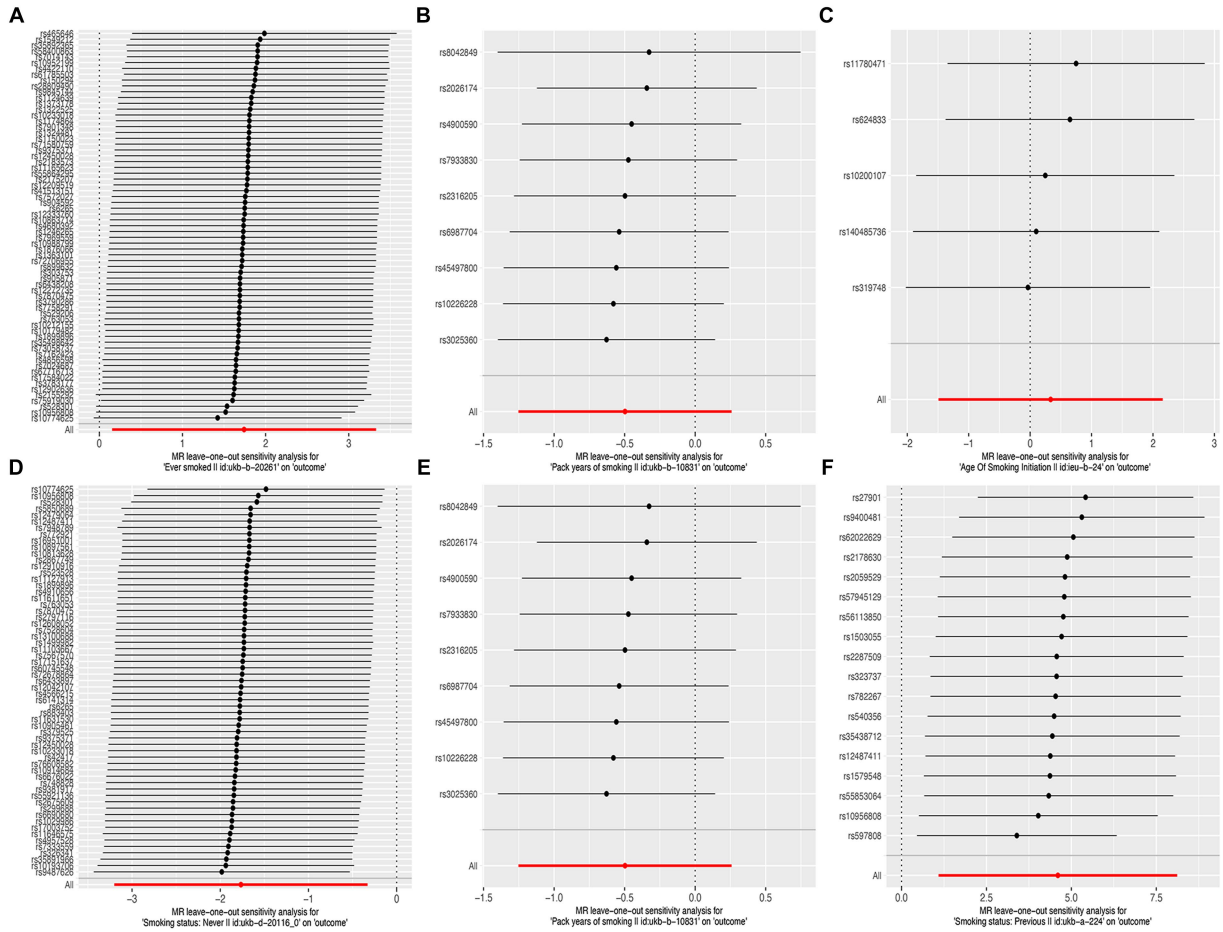

FIGURE 3
Leave-one-out sensitivity analysis of the causal effects of cigarette smoking on liver fibrosis and cirrhosis. **(A)** "Ever smoked"; **(B)** "Pack years of smoking"; **(C)** "Age of smoking initiation"; **(D)** "Smoking status: never"; **(E)** "Smoking status: current"; and **(F)** "Smoking status: previous."

LH: Writing – review & editing. KW: Investigation, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1390049/full#supplementary-material

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Correlation between diameter of esophageal varices and early rebleeding following endoscopic variceal ligation: a multicenter retrospective study based on artificial intelligence-based endoscopic virtual rule

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Background and objective: Bleeding following endoscopic variceal ligation (EVL) may occur as a result of numerous factors, including a diameter of esophageal varices (EV) that is too large to be completely ligated. The present study aimed to develop an artificial intelligence-based endoscopic virtual ruler (EVR) to measure the diameter of EV with a view to finding more suitable cases for EVL.

Methods: The present study was a multicenter retrospective study that included a total of 1,062 EVLs in 727 patients with liver cirrhosis with EV, who underwent EVL from April 2016 to March 2023. Patients were divided into early rebleeding ($n = 80$) and non-rebleeding groups ($n = 982$) according to whether postoperative bleeding occurred at 6 weeks. The characteristics of patient baseline data, the status of rebleeding at 6 weeks after surgery and the survival status at 6 weeks after rebleeding were analyzed.

Results: The early rebleeding rate following 1,062 EVL procedures was 7.5%, and the mortality rate at 6 weeks after bleeding was 16.5%. Results of the one-way binary logistic regression analysis demonstrated that the risk factors for early rebleeding following EVL included: high TB ($P = 0.009$), low Alb ($P = 0.001$), high PT ($P = 0.004$), PVT ($P = 0.026$), HCC ($P = 0.018$), high Child-Pugh score ($P < 0.001$), Child-Pugh grade C($P < 0.001$), high MELD score($P = 0.004$), Japanese variceal grade F3 ($P < 0.001$), diameter of EV ($P < 0.001$), and number of ligature rings ($P = 0.029$).Results of the multifactorial binary logistic regression analysis demonstrated that Child-Pugh grade C ($P = 0.007$), Japanese variceal grade F3 ($P = 0.009$), and diameter of EV ($P < 0.001$) may exhibit potential in predicting early rebleeding following EVL. ROC analysis demonstrated that the area under curve (AUC) for EV diameter was 0.848, and the AUC for Japanese variceal grade was 0.635, which was statistically significant ($P < 0.001$). Thus, results of the present study demonstrated that EV diameter was more optimal in predicting early rebleeding following EVL than Japanese variceal grade criteria. The cut-off value of EV diameter was calculated to be 1.35 cm (sensitivity, 70.0%; specificity, 89.2%).

Conclusion: If the diameter of EV is ≥1.4 cm, there may be a high risk of early rebleeding following EVL surgery; thus, we recommend caution with EVL.

KEYWORDS

liver cirrhosis, esophageal varices, endoscopic variceal ligation, early rebleeding, post-ligation ulcer, artificial intelligence, portal hypertension

1 Introduction

Esophagogastric variceal bleeding (EVB) is one of the most serious and aggressive complications of portal hypertension in liver cirrhosis, and is the leading cause of death in patients with cirrhosis (1). Esophagogastric varices are present in ∼52% of patients with cirrhosis, and varices are present in 50–60% of patients with compensated cirrhosis and up to 85% of patients with decompensated cirrhosis (2). The rate of variceal bleeding is 5–15% per year (3), and the mortality rate after 6 weeks of variceal bleeding is as high as 15–25% (4).

At present, EVL is a first-line treatment method for preventing first EVB (primary prophylaxis), controlling acute esophageal-gastric variceal bleeding, and preventing second EVB (secondary prophylaxis). Notably, EVL is recommended by numerous national and regional gastroenterology and hepatology society guidelines, including those in Europe and America (1, 5–8). Early postoperative rebleeding is a common adverse event associated with EVL, and occurs in 4.8–15.6% of patients following EVL (9–12). Moreover, early postoperative rebleeding may be heavy and uncontrollable, with mortality rates as high as 26.9–38.3% (10–12).

Early rebleeding following EVL is influenced by numerous factors, including an esophageal varices (EV) diameter that is too large to be completely ligated. For complete ligation, and to ensure that the surface mucosa of the target vessel, including the proximal and contralateral walls of the vessel, are completely absorbed into the ligator, EVL is only used for varices of a medium diameter. Moreover, the ligation ring may detach following EVL and fatal rebleeding may occur. Thus, the Chinese Guidelines for Liver Cirrhosis (8) state that an EV diameter of >2.0 cm is a contraindication for EVL, and results of a previous study suggested that an EV diameter >1.0 cm should be included as a contraindication for EVL (13). Notably, the measurement methods for determining the diameter of EV are suboptimal, and there is no reference available in the esophageal lumen. At present, visual assessments are most commonly used for estimating EV diameter; however, these are based on the subjective judgment of endoscopists, and the results may vary depending on prior experience (14).

Selecting different endoscopic treatments according to the diameter of varices aids in the treatment of esophagogastric varices. Thus, a non-invasive measurement technique was developed using endoscopic artificial intelligence (AI); namely, an endoscopic virtual ruler (EVR, Hefei Zhongna Medical Instrument Co., Ltd, Hefei, China) (15), to measure EV diameter without contact. The present study aimed to determine the potential association between the diameter of EV and early rebleeding following EVL, to determine the selection criteria for the appropriate diameter of EV for EVL.

2 Materials and methods

2.1 Clinical data

The present multicenter retrospective cohort study included 727 patients with cirrhosis with EV who underwent EVL from April 2016 to March 2023 in The First Affiliated Hospital of Anhui Medical University, General Hospital of Huainan Oriental Hospital Group and Phoenix Hospital of Huainan Oriental Hospital Group. There was a total of 1,062 EVLs.

Videos and images were available for all cases. During gastroscopy, a transparent cap with an inner diameter of 1 cm (cat. no. DL-108-40; Micro Tech Co., Ltd., Nanjing, China) was installed at the front end of the endoscope to detect the vessel diameter.

The exclusion criteria were as follows: ① Endoscopic treatment of varices, transjugular intrahepatic portosystemic shunt (TIPS), surgical shunts or devascularization surgery within 4 weeks prior to EVL; ② gastric varices treated with tissue glue while implementing EVL; ③ no rebleeding within 6 weeks following EVL and endoscopic treatment of varices, TIPS, surgical shunts or devascularization surgery were performed; ④ patients with active bleeding:Under endoscopy esophageal varices are spurting blood, or oozing so much blood that the field of view is so unclear that it is impossible to apply EVR to accurately measure EV diameter; and ⑤ missing data. The detailed study flow is displayed in Figure 1.

Endoscopic and medical records were reviewed to obtain demographic, clinical, endoscopic and follow-up data. Analyses were conducted to determine the presence of rebleeding at 6 weeks following EVL and death at 6 weeks after bleeding.

The present study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (ethics approval no. PJ2022-10-16). The present study was registered as a clinical trial, with the Chinese Clinical Trial Registry Registration number (trial ID): ChiCTR2200064028(the date of first registration: 24/09/2022). Written consent was obtained from all patients for the endoscopic procedure. Due to the retrospective nature of the present study, the anonymity of data, and the routine nature of all clinical procedures and tests conducted, the requirement for specific informed consent was waived.

2.2 Severity grade of EV

Two grade models were used for the present study:

① Classical morphological assessment

Three physicians with 10 years of endoscopic experience who had carried out >100 EVL cases reviewed the endoscopic features, videos and images of all cases with varices, and graded the

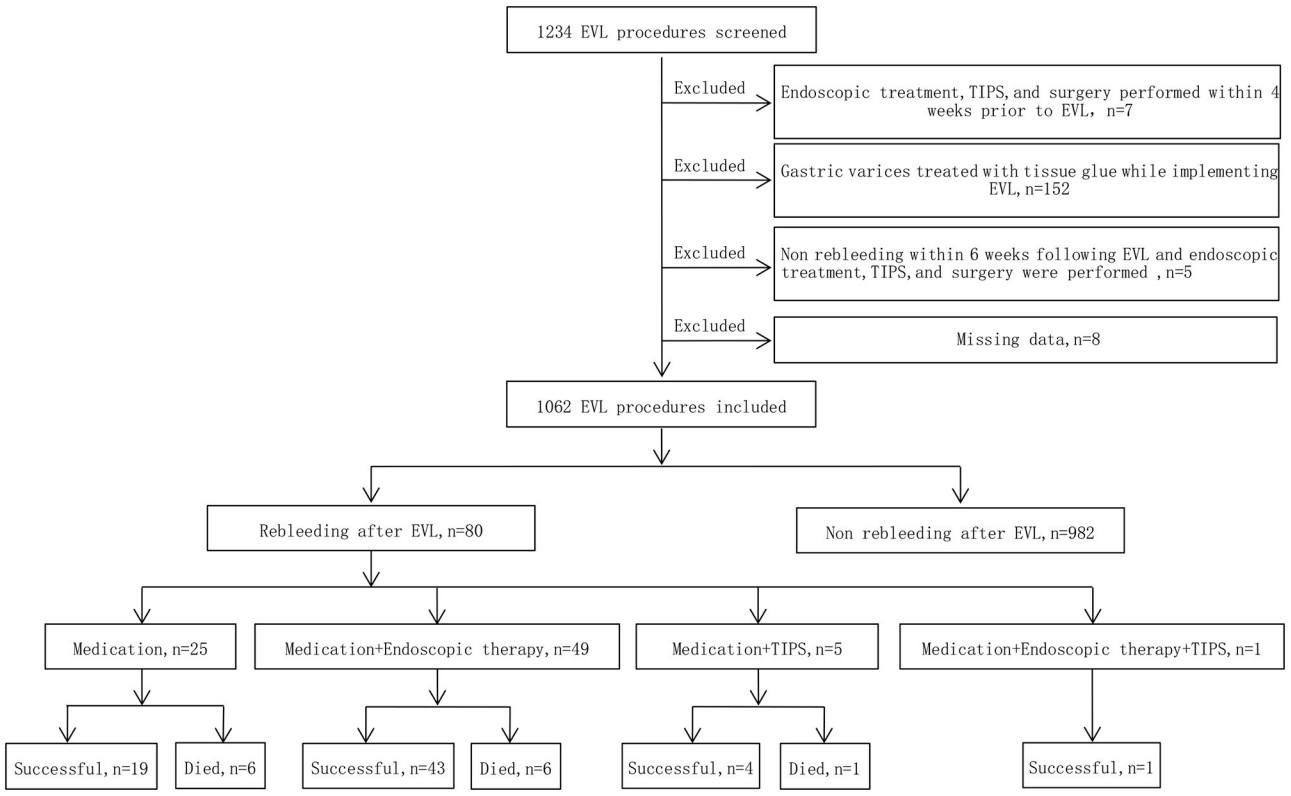

FIGURE 1
Study flow chart. EVL, endoscopic variceal ligation; TIPS, transjugular intrahepatic portosystemic shunt.

varices. According to the guidelines of the Japan Society for Portal Hypertension (16), the grading criteria of EV (referred to as the Japanese variceal grade) are as follows: F1, straight and small-calibered varices; F2, moderately enlarged, beady varices occupying less than one third of the esophageal lumen; and F3, markedly enlarged, nodular or tumor-shaped varices occupying more than one third of the esophageal lumen.

② EVR guides the evaluation of EV diameter

Three physicians, each with over 10 years of endoscopic experience and having performed more than 100 EVL cases, conducted a comprehensive review of the endoscopic features, videos, and images of all cases. They made meticulous observations and precise measurements using EVR. The endoscopic videos and images of all patients were incorporated into the EVR to measure and record the diameter of the largest vessel. EVR is an AI-assisted technique that connects a transparent cap with an inner diameter of 1 cm to the front end of the endoscope to use as a reference. EVR is constructed using algorithms, such as Gaussian filters, Canney Edge detector and Hove circles. Notably, EVR was corrected using a barrel deformation experiment. When approaching the target EV, the discontinuous arc of the cap was detected using AI, and a Cartesian coordinate system was subsequently established in the center of a circle corresponding to the arc (Figure 2). The diameter of EV was determined using the aforementioned coordinate system, and EV size was obtained through reading the scale on a ruler. Retrospective data analysis was performed using EVR software to detect the diameter of EV in endoscopic videos or images. Notably, each endoscopy video used was the original, with a tip cap at the front end of the endoscope. For EV with a diameter >1 cm, the secondary mode of EVR was used. The distance between the anterior cap of the endoscope and the blood vessel was evaluated using the multiplication method to obtain the EV diameter, and this was calculated according to a 1:2 ratio, where a diameter of 2 cm is displayed as 1 cm in EVR. One case of EVR measurement of the variceal diameter by images is displayed in Figure 3. One case of EVR measurement of the variceal diameter by videos is displayed in Supplementary Video 1.

2.3 EVL techniques, main research indicators, and associated concept definitions

EVL was performed in the three hospitals according to standard procedures (17). All EVLs were performed by experienced gastroenterologists with 10 years of endoscopic experience who had carried out >100 EVL cases. The endoscope used exhibited a tip diameter of ∼9.9 mm (cat. no. GIF-Q260J; Olympus Corporation, Japan). The Saeed Six Shooter ligature device was used (cat. no. MBL-6-F; Wilson Cook Medical Incorporated, Winston Salem, NC, USA).Vasoactive drugs (Octreotide or Somatostatin) were uses for 3 days after EVL in all patients with emergency EVLs.

The primary indicator of the present study was postoperative rebleeding at 6 weeks. The secondary indicator of the present study was all-cause mortality at 6 weeks following bleeding, including death due to upper gastrointestinal bleeding, liver failure, hepatic

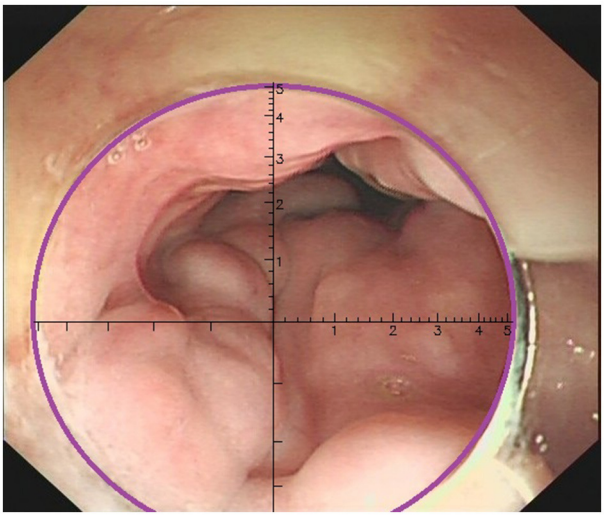

FIGURE 2
The end of the transparent cap was marked as a discontinuous arc in the endoscopic field of view (purple arc on the figure). When the artificial intelligence recognized the arc, it automatically formed a coordinate system.

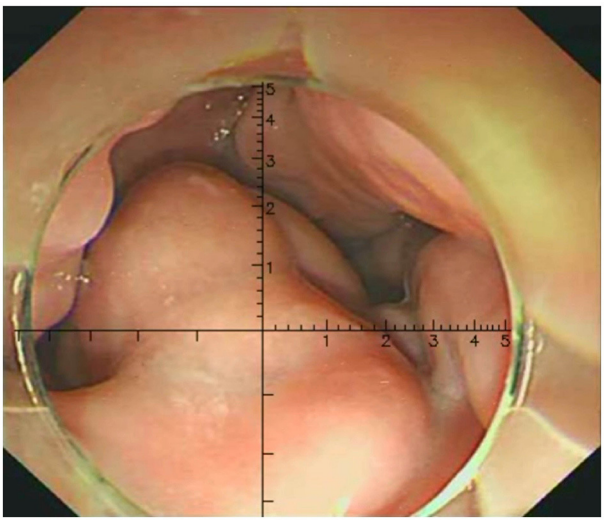

FIGURE 3
Measurement of the EV diameter using EVR by images. The variceal diameter of the patient was about 0.6 cm.

encephalopathy, hepatorenal syndrome or infection. According to the Baveno II (18) standard, any cause of death within 6 weeks of a bleeding episode is considered a bleeding-related death.

Early rebleeding following EVL was defined as recurrence of active bleeding within 6 weeks following EVL. Symptoms of early rebleeding included vomiting blood, black stools or blood in stools; a systolic blood pressure decrease of >20 mmHg or a heart rate increase of >20 beats/min; or a hemoglobin decrease of >30 g/l in the absence of a blood transfusion.

TABLE 1 Characteristics of all patients with 1,062 EVLs included in the present study.

Characteristic	Value
Age, years	55.0 ± 11.6
HGB, g/L	87.4 ± 27.5
PLT, /L	(86.9 ± 75.3) × 10^9
ALT, U/L	40.7 ± 135.1
TB, umol/L	25.0 ± 19.9
Alb, g/L	34.1 ± 5.4
Creatinine, umol/L	66.2 ± 36.7
Blood Na, mmol/L	139.3 ± 3.7
Fasting blood sugar, mmol/L	6.4 ± 2.6
PT, s	15.5 ± 2.7
INR	1.3 ± 0.5
PVT, *n* (%)	204 (19.2%)
HCC, *n* (%)	114 (10.7%)
HE, *n* (%)	20 (1.9%)
Child-Pugh score	7.0 ± 1.7
Child-Pugh grade	
Child A grade, *n* (%)	486 (45.8%)
Child B grade, *n* (%)	478 (45.0%)
Child C grade, *n* (%)	98 (9.2%)
Meld score	9.0 ± 4.1
First EVL, *n* (%)	727 (68.5%)
Not first EVL, *n* (%)	335 (31.5%)
Indications for surgery	
Emergent EVL, *n* (%)	145 (13.7%)
Primary prophylaxis, *n* (%)	139 (13.1%)
Secondary prophylaxis, *n* (%)	778 (73.3%)
Postoperative medication	
Carvedilol, *n* (%)	610 (57.4%)
Propranolol, *n* (%)	43 (4.0%)
None of the above drugs, *n* (%)	409 (38.5%)
Vasoactive drugs, *n* (%)	145 (13.7%)
Vascular fractionation	
EV, *n* (%)	834 (78.5%)
GOV1, *n* (%)	187 (17.6%)
GOV2, *n* (%)	41 (3.9%)
Location	
Upper middle and lower section, *n* (%)	185 (17.4%)
Lower middle section, *n* (%)	591 (55.6%)
Lower section, *n* (%)	286 (26.9%)
RC signs, *n* (%)	952 (89.6%)

(Continued)

TABLE 1 (Continued)

Characteristic	Value
Size of varices	
F1 grade, *n* (%)	64 (6.0%)
F2 grade, *n* (%)	331 (31.2%)
F3 grade, *n* (%)	667 (62.8%)
Diameter of EV, cm	1.0 ± 0.3
Number of ligature rings, n	6.7 ± 2.2

PVT, portal vein thrombosis; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; MELD, model for end-stage liver disease; EVL, endoscopic variceal ligation; EV, esophageal varices; GOV, gastroesophageal varice; RC, red color.

Post-ligation ulcer hemorrhage included postoperative bleeding originating from a post-EVL esophageal ulcer, with an appearance consistent with a banded ulcer and the presence of blood secretion; or a visible blood clot, a pigmented base or blood in the stomach in the absence of alternative sources of upper gastrointestinal bleeding.

2.4 Statistical analysis

Statistical analyses were performed using SPSS (version 26.0; IBM©Corp., Armonk, NY, USA). Quantitative data are expressed as the mean ± standard deviation (x ± s), and qualitative data are expressed as frequencies and percentages. Consistency within and between groups was analyzed using intraclass correlation efficient (ICC) for physician visual assessment and EVR measurement of esophageal variceal diameter. The potential association between Japanese variceal grade and esophageal variceal diameter measured using EVR with early rebleeding following EVL was determined using one-way binary logistic regression. The predictive ability of either Japanese variceal grade or esophageal variceal diameter on early rebleeding following EVL was further assessed using receiver operating characteristic (ROC) curves. AUC >0.6 indicated an average level of accuracy, and AUC >0.8 indicated a high level of accuracy. $P < 0.05$ was considered to indicate a statistically significant difference.

3 Results

3.1 Basic patient characteristics

A total of 727 patients were included in the present study, including 498 males and 229 females. Notably, there were 410 cases of liver cirrhosis caused by hepatitis B, 15 cases of liver cirrhosis caused by hepatitis C, 67 cases of alcoholic cirrhosis, 33 cases of hepatitis B and alcohol, 4 cases of hepatitis C and alcohol, 65 cases of autoimmune disease, 11 cases of schistosomiasis, and 122 cases with unknown causes. A total of 1,062 EVL procedures were performed. The baseline indicators of patients are displayed in Table 1.

3.2 Distribution of esophageal variceal diameter

Patients included in the present study exhibited an approximate normal distribution, with the majority of cases exhibiting a peak EV diameter of 0.9 cm. The distribution of EV diameters is displayed in Figure 4.

3.3 Consistency within and between two groups

An analysis using intraclass correlation efficient (ICC) was performed and found that the intraclass correlation efficient between physician visual assessment and EVR measurement of EV diameters was 0.815, and that the intraclass correlation efficient among the three physicians' visual assessment of EV diameters was 0.870, and the intraclass correlation efficient among the three physicians' measurements of EV diameters using the EVR was 0.965.

3.4 Early postoperative rebleeding rate and mortality

There were 80 cases of early postoperative rebleeding at 6 weeks with a bleeding rate of 7.5% (80/1,062), including 1 case of postoperative bleeding in grade F1 patients, 9 cases of postoperative bleeding in grade F2 patients and 70 cases of postoperative bleeding in grade F3 patients. The bleeding rate was 11.0% (16/145 patients) following emergency EVLs, while the bleeding rate observed following prophylactic EVLs was 7.0% (64/917). The postoperative bleeding rate following emergency EVLs was higher than that of prophylactic EVLs; however, the difference was not statistically significant ($P = 0.088$).

Despite additional medication, endoscopic treatments or TIPS, 13 patients with postoperative bleeding died in the present study. Among 80 cases of bleeding following EVL, 1 patient experienced two early bleeding episodes following EVL. The 6-week mortality rate following a bleeding episode was 16.5% (13/79 patients). In the present study, numerous patients did not undergo endoscopy and treatment due to effective medication or unstable vital signs due to heavy bleeding. Among 50 patients with postoperative bleeding who underwent endoscopic diagnosis and treatment, 42 cases of bleeding originated from ulcers following ligation, and 8 cases of bleeding originated from ruptured EV that were not occluded.

3.5 Predictive potential of EV diameter for early rebleeding following EVL

In a one-way binary logistic regression analysis of the patients' relevant data, various factors were examined to determine their association with early rebleeding following EVL. The analysis revealed several significant risk factors. These included high total bilirubin (TB) levels ($P = 0.009$), low albumin (Alb) levels ($P = 0.001$), elevated prothrombin time (PT) ($P = 0.004$), presence

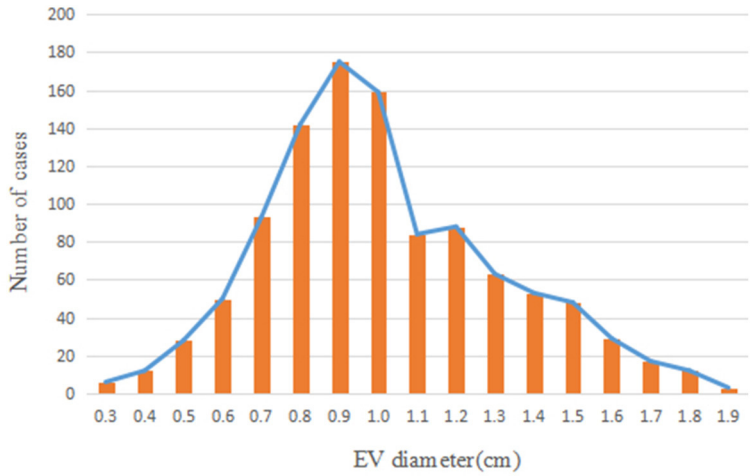

FIGURE 4
Distribution map of EV diameters. EV, esophageal varices.

of portal vein thrombosis (PVT) ($P = 0.026$), hepatocellular carcinoma (HCC) ($P = 0.018$), high Child-Pugh score ($P < 0.001$), Child-Pugh grade C ($P < 0.001$), high Model for End-Stage Liver Disease (MELD) score ($P = 0.004$), Japanese variceal grade F3 ($P < 0.001$), diameter of EV ($P < 0.001$), and number of ligature rings used ($P = 0.029$) (Table 2). These findings underscore the importance of considering these factors in the management and risk assessment of patients undergoing EVL.

Variables with $P < 0.05$ in one-way logistic regression analysis further selected: high TB, low Alb, PVT, HCC, high Child-Pugh score, Child-Pugh grade C, high MELD score, Japanese variceal grade F3, diameter of EV, and number of ligature rings were included in multifactorial binary logistic regression analysis. The results showed that the independent influences of early rebleeding following EVL were Child-Pugh grade C ($P = 0.007$), Japanese variceal grade F3 ($P = 0.009$), and diameter of EV ($P < 0.001$) which may exhibit potential in predicting early rebleeding following EVL.

Results of the ROC analysis revealed that the EV diameter AUC was 0.848 (95% CI, 0.797–0.899; $P < 0.001$), and the Japanese Variceal grade AUC was 0.635 (95% CI, 0.580–0.690; $P < 0.001$), as shown in Figure 5. Results of further statistical analysis demonstrated that the predictive value of EV diameter for early postoperative rebleeding was greater than that of Japanese Variceal grade [z = 10.991; Sig. (2-tail)[a] = 0; AUC difference, 0.213; standard error (SE) difference[b] = 0.213, asymptotic 95% CI, 0.175–0.251]. EV diameter is a continuous variable, and the cut-off value was determined as 1.35 cm, with a sensitivity of 70.0% and a specificity of 89.2%. In the present study, the relatively low sensitivity may be associated with the lower early postoperative rebleeding rate of 7.5%.

4 Discussion

Stiegmann et al. (19) initially carried out EVL in the treatment of esophageal variceal bleeding in 1986. Subsequently, EVL was compared with endoscopic injection sclerotherapy (EIS), and results demonstrated that adverse events were reduced at a higher level following EVL; thus improving survival, eliminating varices and reducing rebleeding rates (20, 21). Therefore, EVL is selected as the preferred option for the endoscopic treatment of EV. However, EVL may exert potentially fatal adverse events, such as early rebleeding following EVL. Results of the present study demonstrated that the rebleeding rate at 6 weeks following EVL was 7.5%, and the mortality rate at 6 weeks following bleeding was 16.5%. Results obtained by Sarin et al. (22) highlighted that bleeding following EVL may be a result of post-ligation ulcers, ruptured unoccluded EV, bleeding from ruptured gastric varices or portal hypertensive gastropathy. Notably, results of previous studies demonstrated that ulcers were not the main source of early rebleeding following EVL (10); however, numerous studies demonstrated the opposite results (12, 23, 24). Thus, in recent years, research is focused on adverse events following EVL, such as post-ligation ulcer hemorrhage. Notably, EVL is a standardized method that pre-sets the volume of varices that are absorbed into the cylinder for ligation. EVL is limited by the capacity of the ligation device; thus, only ligating the mucosa and submucosa (25). Shallow ulcers and inflammatory infiltration above the superficial submucosa may form once the ligated tissues at the EVL treatment site are shed. Notably, the ulcers are round with a white fibrin base, with a diameter of 10–12 mm and a depth of 1–2 mm. Ulcers often heal within 2–3 weeks (26). All EVLs result in postoperative ulcers; however, postoperative bleeding does not occur following every EVL. A high severity of liver disease and high blood sugar may result in the poor healing of ulcers; thus, postoperative bleeding (11, 27, 28). Our study found that Child-Pugh grade C, Japanese variceal grade F3, and diameter of EV may exhibit potential in predicting early rebleeding following EVL. On the other hand, postoperative bleeding may only occur when EV is too large for the vessels to be completely ligated, leading to ligature ring detachment and exposure of broken vessels below the ulcer (9). The Chinese Guidelines for Liver Cirrhosis (8) indicate that EV

TABLE 2 One-way binary logistic regression analysis of risk factors for early rebleeding following EVL.

Variable		Non-rebleeding ($n = 982$)	Rebleeding ($n = 80$)	*P*	OR
Sex	Female, *n*	310	21		
	Male, *n*	672	59	0.325	0.772
Age, years		55.0 ± 11.5	56.0 ± 12.2	0.445	1.008
Causes of cirrhosis	Viral hepatitis, *n*	566	42		
	Acohol, *n*	100	3	0.136	0.404
	Viral hepatitis+alcohol, *n*	55	7	0.212	1.715
	Autoimmune, *n*	92	10	0.301	1.465
	Other reasons, *n*	169	18	0.221	1.435
HGB, g/L		87.8 ± 27.5	82.5 ± 27.2	0.091	0.992
PLT,/L		$(87.0 \pm 76.4) \times 10^9$	$(85.8 \pm 60.5) \times 10^9$	0.888	1
ALT, U/L		40.8 ± 140.1	38.5 ± 38.2	0.882	1
TB, umol/L		24.5 ± 19.8	30.8 ± 20.5	0.009	1.011
Alb, g/L		34.2 ± 5.4	32.2 ± 5.6	0.001	0.934
Creatinine, umol/L		66.4 ± 36.8	64.0 ± 35.9	0.582	0.998
Blood Na, mmol/L		139.3 ± 3.8	139.2 ± 3.4	0.914	0.997
Fasting blood sugar, mmol/L		6.4 ± 2.6	6.6 ± 2.1	0.360	1.038
PT, s		15.4 ± 2.6	16.3 ± 3.6	0.004	1.099
INR		1.3 ± 0.5	1.3 ± 0.2	0.415	1.143
PVT, *n*		181	23	0.026	1.786
HCC, *n*		99	15	0.018	2.058
Large amount of ascites, *n*		16	3	0.182	0.425
None+small+moderate amount of ascites, *n*		966	77		
HE, n		17	3	0.213	2.212
Child-Pugh score		6.9 ± 1.7	8.0 ± 2.0	0	1.360
Child-Pugh grade C, *n*		71	27	0	6.537
Child-Pugh grade A+B, *n*		911	53		
Meld score		8.9 ± 4.1	10.3 ± 4.0	0.004	1.077
Not first EVL, *n*		309	26	0.848	1.049
First EVL, *n*		673	54		
Indications for surgery	Emergent EVL, *n*	129	16	0.088	1.653
	Prophylactic EVL, *n*	853	64		
Postoperative medication	Carvedilol, *n*	567	43	0.749	0.925
	Propranolol, *n*	37	6	0.154	1.977
	None, *n*	378	31		
Vasoactive agents, *n*		129	16	0.088	1.653
Vascular fractionation	EV, *n*	774	60	0.674	
	GOV1, *n*	170	17	0.376	1.290
	GOV2, *n*	38	3	0.976	1.018
Location	Upper middle and lower section, *n*	166	19		

(Continued)

TABLE 2 (Continued)

Variable		Non-rebleeding ($n = 982$)	Rebleeding ($n = 80$)	P	OR
	Lower middle section, n	547	44	0.221	0.703
	Lower section, n	269	17	0.088	0.552
RC signs, n		879	73	0.624	1.222
Japanese variceal grade	F3, n	597	70	0	4.514
	F1+F2, n	385	10		
Diameter of EV, cm		1 ± 0.3	1.4 ± 0.3	0	171.186
Number of ligature rings, n		6.7 ± 2.1	7.2 ± 2.8	0.029	1.102

EV, esophageal varices; EVL, endoscopic variceal ligation; OR, odds ratio.

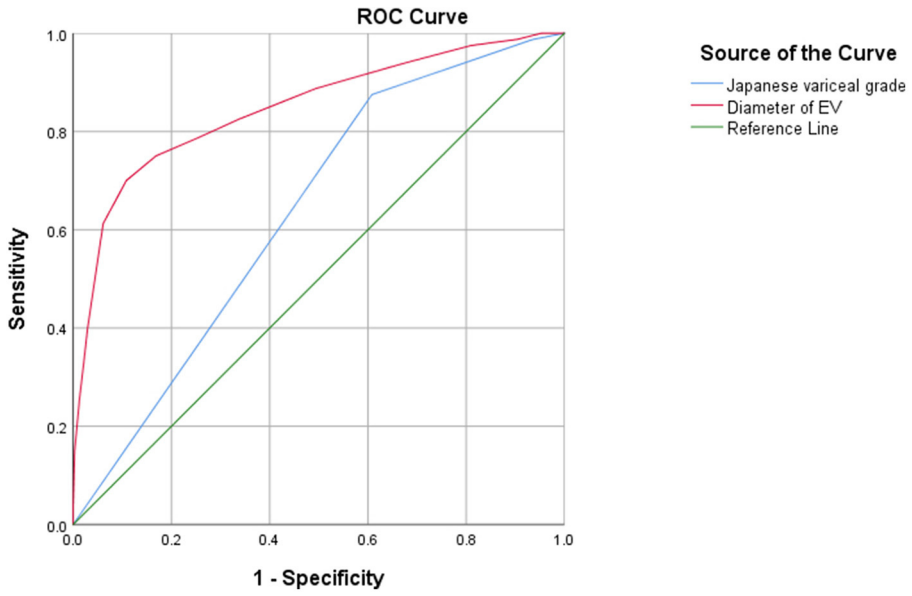

FIGURE 5
EV diameter and Japanese variceal grade as predictive factors for early rebleeding following EVL.

with a diameter >2.0 cm is not suitable for EVL. However, the diameter of blood vessels is judged by independent examiners and is therefore subjective, and the exact diameter may not be accurately stated. Therefore, the misjudgment of endoscopists may lead to inappropriate ligation and bleeding events following EVL.

At present, research into the impact of EV diameter on early bleeding following EVL is limited. Results of the present study revealed a high risk of early rebleeding following EVL in patients with EV Japanese variceal grade F3 and a large EV diameter. Despite additional medication, endoscopic treatment and TIPS following bleeding, 13 people died in the present study. Notably, the 6-week mortality rate following bleeding was 16.5%. In addition, there were 667 cases of grade F3 varices, with an early postoperative rebleeding rate of 10.5% (70/667). Thus, not all grade F3 EVs were suitable for EVL. EVR was subsequently used to measure the diameter of EV, and further statistical analysis revealed a cut-off value of 1.35 cm. Results of the present study demonstrated that the probability of early bleeding following EVL in patients with an EV diameter ≥1.4 cm was 34.6% (56/162). Considering the differences in ligation levels and the potential errors in assessment of variceal diameters, we recommend caution with EVL if the EV diameter is ≥1.4 cm. The percentage of patients with an EV diameter of ≥1.4 cm was relatively small, accounting for 15.3% (162/1,062) of patients included in the present study.

During successful EVLs, the static inner diameter and retraction force of the rubber band are equal, and the early detachment of the ligation ring is associated with the size of the EV. Prior to the formation of variceal thrombosis, if the rubber band detaches prematurely, the ligation site histologically demonstrates mucosal necrosis, vascular necrosis and the continuous dilation of varices; thus, the risk of bleeding remains high (29). Chen et al. (30) reported 7 cases of hemorrhage from 15 h to 9 days following EVL, which were considered to be associated with large varices, with a diameter exceeding the maximum diameter that should be ligated. During ligation, not all varices are absorbed into the cylinder of the ligature; thus, the entire vein is not ligated and blood flow is not completely blocked. This may lead to a lack of secondary thrombosis, slipping of the ligature ring and hemorrhage. Thus,

EVL requires complete ligation. Ligation of the mucosa and the entire blood vessel, including the contralateral blood vessel wall, is required to achieve complete ligation effects and prevent the ligation ring from detaching. At present, the six-ring ligation device is widely used in clinical practice, with a diameter of ~10 mm and a front cylinder length of ~10 mm. Notably, the ligation volume depends on the corresponding cylinder, not on the elasticity of the band (31). Therefore, the maximum diameter of the varices that can be ligated by the ligation device is limited to a certain range. Li et al. (13) demonstrated that the diameter of the porcine varices impacted the degree of complete ligation *in vitro*, and the larger the diameter, the lower the proportion of complete ligation. Results of the present study demonstrated that large varices which exceed the maximum diameter for ligation may lead to early detachment of the ligature ring; thus, impacting healing of the ulcer, leading to heavy bleeding. Therefore, EVs that are too large are not suitable for ligation.

The most important factor for the prediction of variceal bleeding in cirrhotic portal hypertension is the size of the varices, and the risk of bleeding in patients with large varices is as high as 17% per year (32). The American Association for Liver Research recommends using a two-level classification system to determine the size of EV, and proposed a 5-mm threshold to classify varices into small and large groups. Thus, treatment and follow-up strategies are selected in line with varices size. Notably, accurate measurement of EV diameter, and the correct classification of large and small veins is required, for selecting treatment strategies and monitoring follow-up. A non-invasive measurement technique with endoscopic AI; namely, EVR, was used in the present study. In this study, consistency within and between groups was analyzed using intraclass'g correlation efficient (ICC) for physician visual assessment and EVR measurement of esophageal variceal diameter. The results showed that the intraclass correlation efficient for measuring esophageal variceal diameters using EVR were higher than that for visual assessment, suggesting that EVR measurements are highly consistent and more reliable. Notably, EVR exhibits multiple advantages, including increased levels of accuracy in detecting and measuring EV diameter, as demonstrated in a previous study (15). In addition, EVR is user-friendly, as additional equipment and instruments are not required. EVR is cost-effective, time-efficient and does not impose additional burden or risk on the patient. Moreover, as a virtual measurement tool, EVR may be used to retrospectively measure the diameter of varices, as well as measuring in real-time during endoscopic examination. EVR is useful software for the endoscopic detection and treatment of EV, and allows endoscopists to objectively measure the variceal diameter; thus, assessing the risk of bleeding. In addition, EVR may provide an important reference for selecting an appropriate treatment strategy.

Although the present study is a multicenter and large-scale study, there are numerous limitations. For example, follow-up was limited in some patients due to the retrospective nature of the present study. In addition, the distance between the front cap of the endoscope and the varices is uncontrollable, and the transparent cap of the endoscope must be placed close to the target vessel. Moreover, not all endoscopists use a transparent cap in experimental procedures, and EVR detection cannot be carried out without a transparent cap. Therefore, improvements in EVR technology and further studies with larger sample sizes are required.

In conclusion, post-ligation ulcer hemorrhage is an adverse event associated with EVL, and the associated mortality rate is high. We recommend caution with EVL if the EV diameter is $\geq$1.4 cm because of the high risk of early rebleeding following EVL surgery, and alternative treatments, such as non-selective beta blockers, TIPS and EIS maybe should be considered. Notably, the technology of EIS is inconsistent, which may impact the potential therapeutic effects. The development of novel instruments and technologies may significantly improve the efficacy of EIS (33); however, further investigations are required.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because the retrospective nature of the present study, the anonymity of data, and the routine nature of all clinical procedures and tests conducted, the requirement for specific informed consent was waived. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CC: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. JJ: Data curation, Writing – review & editing. RC: Data curation, Formal analysis, Writing – original draft. YC: Data curation, Writing – original draft. KW: Supervision, Writing – original draft. ZW: Data curation, Writing – original draft. TX: Data curation, Writing – original draft. HZ: Data curation, Writing – original draft. HH: Data curation, Writing – original draft. HL: Data curation, Validation, Writing – original draft. QZ: Data curation, Validation, Writing – review & editing. XM: Data curation, Supervision, Writing – original draft. DK: Methodology, Supervision, Validation, Writing – review & editing.

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Conflict of 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1406108/full#supplementary-material

SUPPLEMENTARY VIDEO 1
Measurement of the EV diameter using EVR by videos. The variceal diameter of the patient was about 0.6 cm.

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Case report: Management of liver cancer complicated by gastric varices rupture and bleeding: transjugular intrahepatic portosystemic shunt utilizing the mesenteric venous pathway

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To avoid recurrent variceal bleeding, transjugular intrahepatic portosystemic shunt (TIPS) in conjunction with variceal embolization is considered to be an effective strategy. However, due to changes in conditions and variations in the patient's state, individuals undergoing TIPS may face challenges and limitations during procedures. The transjugular technique and combined transsplenic portal venous recanalization (PVR) with TIPS were not effective in this case due to a blocked portal vein and a previous splenectomy. With an abdominal incision, we successfully punctured the mesenteric venous system and navigated the occluded segment of the portal vein through the mesenteric approach. TIPS was then performed under balloon guidance. This study aims to explore the management of risks and complications during surgical operations and propose multiple preoperative surgical techniques to improve the success rate of the procedure.

KEYWORDS

TIPS, interventional, portal hypertension, portal vein thrombosis, hepatocellular carcinoma

1 Introduction

Decompensated liver cirrhosis can result in severe vertical hemorrhage, with high mortality rates despite recent improvements in survival. A multidisciplinary approach is necessary to treat gastrointestinal bleeding in patients with advanced liver cirrhosis (1). Various therapies are used to prevent and manage shock, with additional goals of resuscitation and supportive care (2). Advanced liver cirrhosis requires a multidisciplinary approach to improve survival rates (3).

Persistent portal vein thrombosis (PVT) poses significant challenges, especially in patients with hepatocellular carcinoma (HCC) and a history of splenectomy. Transjugular intrahepatic portosystemic shunt (TIPS) is often utilized to reduce portal hypertension and manage variceal bleeding effectively. Despite technical difficulties and potential complications, TIPS remains a viable option for PVT treatment (4–6). However, the presence of PVT complicates conventional TIPS procedures as the occlusion of the portal vein limits the pathways for puncture and stent placement. Qi et al. (7) highlighted several approaches for TIPS placement in PVT patients, including transjugular, transhepatic,

transsplenic, and transmesenteric methods. Although the mesenteric approach is less frequently used due to its specialized nature and higher risk, it becomes crucial when other routes are not feasible. Rossle et al., Blum et al., and Edelson et al. (8–10) emphasized the importance of TIPS in managing variceal bleeding and its complications. Despite certain complications such as hepatic encephalopathy, these are usually manageable. Literature reviews indicate that the long-term outcomes of TIPS are favorable, even with higher rates of stenosis and occlusion, as early detection and intervention can effectively prevent severe consequences. Bilbao et al. (11) explored the limitations of percutaneous methods in treating PVT, including fibrinolytic infusion, balloon angioplasty, and stent placement. Their studies showed that while these methods achieved clinical improvement in some acute PVT cases, the morphological results were not always ideal, with some patients experiencing re-thrombosis. This underscores the importance of selecting appropriate treatment methods in complex PVT cases. Rozenblit et al. (12) and Rozenblit et al. (13) proposed a combined transmesenteric and transfemoral approach for TIPS placement, integrating radiological and surgical techniques. They demonstrated successful cases of accessing the portal vein system through a small incision in the mesenteric vein in complex cases. This method improves instrument control and surgical efficiency, thereby reducing operation time and radiation exposure while providing better portal system evaluation. Entezari et al. (14), Dewald et al. (15), and Chamsuddin et al. (16) further expanded this technique by introducing a combined transmesenteric and transjugular approach (Meso-TIPS) for treating complex PVT cases, proving its efficacy and safety.

In our case report, a patient with decompensated liver cirrhosis, HCC, and a history of splenectomy presented with persistent PVT. Given the extensive thrombosis and exclusion of splenic access, the mesenteric route was the only viable option for TIPS placement. This method, underscores the feasibility and safety of the mesenteric pathway in complex PVT cases, aligning with the findings of previous studies (7, 12–16). The successful implementation of TIPS through the mesenteric route in this patient demonstrates a crucial therapeutic strategy for managing severe portal hypertension and its associated complications. This study emphasizes the importance of selecting appropriate access routes and using advanced imaging and thrombectomy techniques in managing complex PVT cases. By applying these advanced techniques to our case report, we highlight the reliability and efficacy of the mesenteric approach for TIPS. This approach not only addresses major clinical challenges but also improves the patient's long-term prognosis, thereby rendering our treatment strategy more credible and successful.

2 Case report

Patient History: The patient has a history of liver cirrhosis, hepatitis B, and a splenectomy performed in 2012. In April 2023, HCC was detected, accompanied by PVT, hypertension, and alterations in the portal vein. The initial Barcelona Clinic Liver Cancer (BCLC) staging was B-C due to thrombus uncertainty and carcinoma concerns. Before admission, the patient experienced gastrointestinal bleeding. On 13 November, 2023, varices were detected during an esophagogastroduodenoscopy. On 16 November, 2023, an enhanced CT scan showed no significant changes in the tumor compared to the initial CT scan. However, abnormal perfusion patterns were seen around it, mostly in liver segments I, VI, and VII (see Figure 2A). The liver is affected by cirrhosis, and the spleen has been removed. The portal vein is occluded and demonstrates fibrosis, with collateral circulation present. Additionally, there is mild intrahepatic bile duct dilation and fluid accumulation in the abdomen (see Figure 2B).

A multidisciplinary discussion ruled out band ligation for variceal bleeding due to its risk and ineffectiveness. Consequently, a TIPS procedure was selected as an alternative intervention. Initially, attempts through the jugular vein pathway failed, leading to the involvement of the surgery and anesthesia departments to execute the modified TIPS strategy. An 8-mm Viatorr-coated stent (W. L. Gore & Associates, Flagstaff, Arizona, USA) was used to create a shunt channel extending from the proximal hepatic vein to the main portal vein. Considering the patient's long-standing PVT and local narrowing of the mesenteric veins, the stent placement area was extended during the procedure using an 8-mm smart bare metal stent (Cordis Corporation, Milpitas, California, USA). Throughout the procedure, the partial pressure gradient (PPG) remained below 10 mm Hg. Prior to the TIPS development, the PPG was 10 mm Hg. The Viatorr TIPS-covered stent (7 cm polytetrafluoroethylene cover and 2 cm bare metal segment) was inserted into the portal vein, dilated to 8 mm, reducing the PPG to 4 mmHg. The stent's upper end (6-cm bare metal stent) extended to the border between the liver and the heart. The intestinal mesenteric thrombus was cleared during the procedure, with no persistent thrombosis detected. Subsequent angiography showed significant local mesenteric vein stenosis. To prevent postoperative thrombosis and associated complications, the narrowed segment was dilated with a balloon, and an 8-cm bare metal smart stent was placed to restore potency in the narrowed area of the mesenteric vein, as shown in the picture. After surgery, the patient developed pneumonia. A chest X-ray on 29 November 2023, 2023 showed bilateral inflammatory infiltrates with slight left lower lung field progression since 22 November, 2023. The patient's condition improved with treatment. Subsequent CT scans showed favorable outcomes without signs of gastrointestinal bleeding or hepatic encephalopathy.

3 Discussion

Patients with decompensated liver cirrhosis and malignant liver tumors, particularly those experiencing gastric variceal bleeding, face a poor prognosis. As discussed in the introduction, gastric variceal bleeding is a leading cause of mortality, primarily due to recurrent bleeding and liver failure (17). The coexistence of HCC, portal hypertension, and bleeding gastric varices complicates TIPS procedures. As highlighted in the introduction, TIPS is effective in managing clinically significant portal hypertension (CSPH) and HCC, with high success rates and minimal complications (18). Studies have demonstrated that combining TIPS with local treatments can prolong survival in HCC patients with portal hypertension (19). This aligns with the introduction's discussion on the multidisciplinary approach required for effective management of advanced liver cirrhosis. TIPS is a safe and effective method for HCC patients with symptomatic portal hypertension. TIPS should

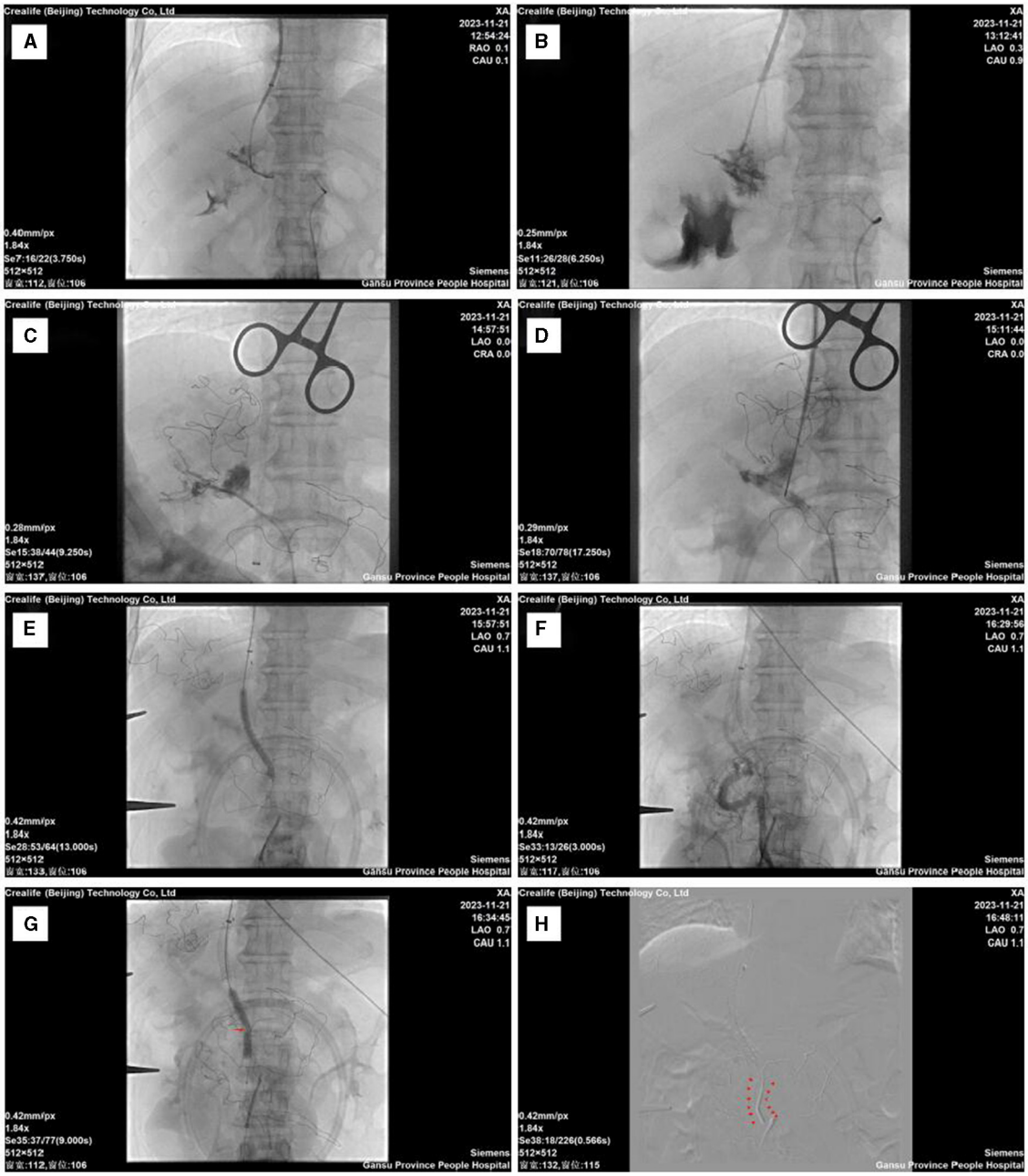

FIGURE 1
Intraoperative imaging data. **(A)** Successful puncture through the conventional approach. **(B)** Local rupture of the portal vein after multiple punctures. **(C)** Guidewire-assisted catheterization through the mesenteric route into the right branch of the portal vein. **(D)** Balloon-guided puncture technique. **(E)** Balloon dilation of the puncture tract and placement of the stent, followed by local balloon dilation within the stent. **(F)** Post-stent placement angiography reveals mesenteric thrombus. **(G)** Mesenteric venous stenosis balloon angioplasty. **(H)** Extended placement area of the mesenteric stent.

be considered for cases of HCC, especially for managing variceal bleeding or as a temporary measure in patients who are unable to undergo HCC treatment due to ascites or portal hypertension. TIPS can still be used for individuals with advanced liver cirrhosis and other health problems, even if they are also diagnosed with HCC.

Initially, the conventional TIPS approach was considered but was not successful. Fluoroscopic imaging was used to confirm entry into the portal vein (Figure 1A), but the shunt channel could not be created. There was a local rupture and bleeding of the portal vein during the surgery (Figure 1B). This difficulty highlights the challenges mentioned in the introduction about the complexity of PVT in TIPS procedures. Multiple attempts to create a shunt channel through the thrombotic segment were unsuccessful, likely due to the chronic nature of the disease. Consequently, conventional interventional techniques were discontinued to minimize additional risks.

Placing a TIPS is particularly challenging in cases of splenic and portal vein obstructions, increasing the risk of complications

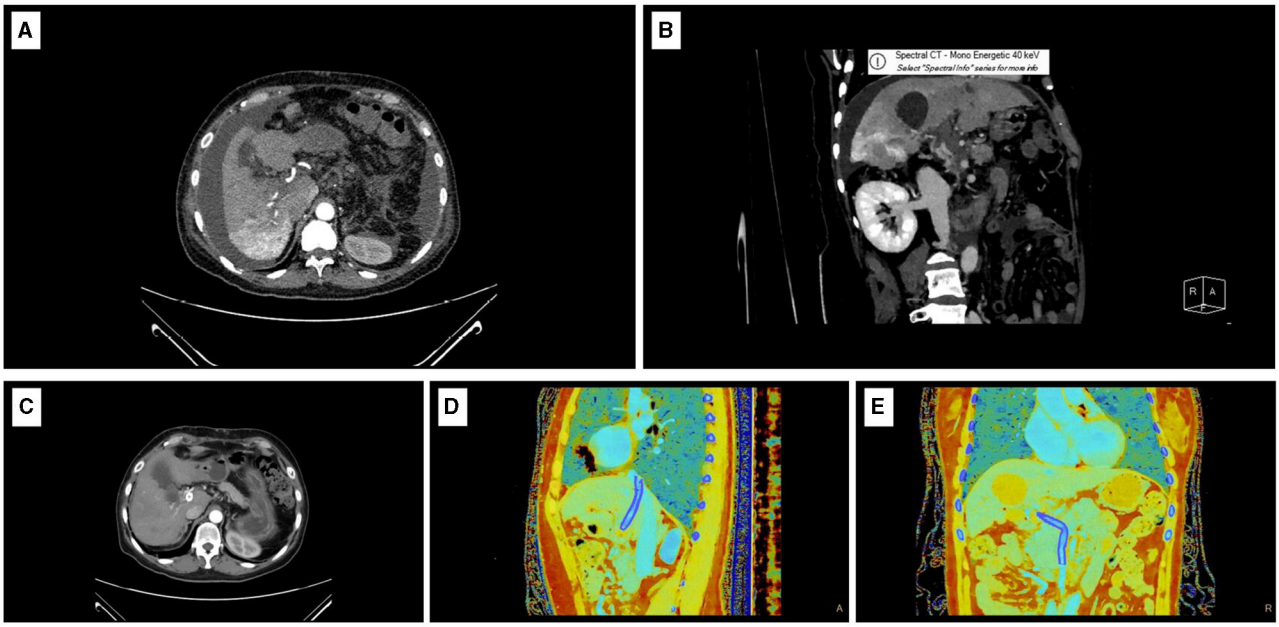

FIGURE 2
Imaging data. **(A)** Preoperative CT-enhanced arterial phase transverse image. **(B)** Preoperative CT-enhanced portal venous phase coronal image. **(C)** Postoperative CT-enhanced arterial phase transverse image. **(D)** Sagittal effective atomic number map on postoperative CT. **(E)** Coronal effective atomic number map on postoperative CT.

and procedural complexity. This difficulty was anticipated in the introduction, which discusses the limitations of conventional access routes in the presence of extensive PVT. However, literature reviews, such as the one by Yan et al., unanimously conclude that TIPS for PVT is feasible and safe (7, 20). Portal vein obstruction should not be viewed as an absolute contraindication for TIPS (21). This is in line with the assertion made in the introduction that despite complications, TIPS remains a viable option for managing variceal bleeding and portal hypertension. TIPS procedures have been successfully performed in patients with portal vein occlusion due to thrombosis. TIPS has shown good efficacy in cases involving PVT (4, 22). The patient, experiencing severe portal vein blockage, underwent a splenectomy before the TIPS procedure. This necessitated ruling out traditional routes such as transjugular or splenic veins. The theoretical advantages of TIPS for PVT are deemed substantial, given its capacity for vascular restoration and prevention of thrombotic events and its associated complications through enhanced portal vein hemodynamics (23, 24). Different strategies and techniques have been developed to tackle challenges posed by chronic portal vein and splenic vein blockages. For PVR-TIPS, where a balloon-assisted shunt is created in the portal vein, ultrasound can guide a needle through the superior mesenteric vein (SMV) when direct liver or spleen access is not possible (15). The transjugular approach can cause problems during TIPS procedures. To avoid these problems, both the mesenteric and transjugular venous pathways can be used at the same time (14). This method has been shown to be feasible and effective for individuals with difficult splenic vein access (12, 13). It did not cause any acute issues, and follow-up imaging demonstrated positive outcomes with the placement of an intrahepatic portosystemic shunt (IPS) (25).

After thorough planning, a surgical strategy was devised. Transitioning swiftly to our backup plan when traditional methods failed, we encountered challenges with ultrasound-guided punctures on the mesenteric vein, specialized equipment needs, and limited expertise, prompting us to halt this method. Instead, we opted for the MAT (Mesenteric Approach Technique) method for performing TIPS with assistance from a small incision under general anesthesia. MAT-TIPS has also been successfully used in cirrhotic patients whose portal vein is completely blocked due to chronic thrombosis. This method presents a novel approach to conduct TIPS in these situations (26). It has been shown to have similar effects on intrahepatic shunt function and to cause similar complications during surgery as the standard transjugular method (27). The second surgical approach entailed higher risks and increased complexity. Despite encountering challenges, the procedure was successful. A small incision was made in the abdomen to access the abdominal cavity. Contrary to the intended target of the SMV, the inferior mesenteric vein was inadvertently punctured. Nevertheless, the surgery proceeded smoothly, and the catheter successfully reached the portal vein (Figure 1C). A balloon-assisted puncture technique was employed to facilitate the advancement of the balloon into the portal vein. The puncture needle was navigated through the jugular vein and directed toward the balloon for insertion. Subsequently, a guidewire was threaded through the balloon catheter and carefully maneuvered across the thrombotic segment (Figure 1D). The surgical plan, including stent placement and balloon dilation, was followed step by step (Figure 1E). Everything proceeded as planned.

First, we placed a Viatorr-coated stent within the established TIPS channel, navigating through the occluded segment of the portal vein. Immediate local contrast imaging revealed some

thrombus formation in the mesenteric veins (Figure 1F). In this study, several factors were identified to be increasing the likelihood of acute mesenteric venous thrombosis (MVT), including smoking, high blood pressure, peritonitis, hemoglobin levels, albumin levels, intraperitoneal free fluid, decreased intestinal wall enhancement, and bowel distension (28). Additionally, factors such as a history of blood clotting problems, splenectomy, and symptoms like nausea, vomiting, abdominal pain, tenderness, and distension, along with lab results showing high plasma lactate levels and white blood cell counts, must be considered (29). The patient's history and examination results indicated several of these risk factors, including intra-abdominal fluid accumulation, hypoalbuminemia, and anemia. The patient's prior splenectomy further contributed to the development of MVT. Several factors influence the prognosis of acute MVT. However, early diagnosis and anticoagulant therapy can lead to rapid improvement in clinical symptoms (30). In cases of trauma-related MVT, standalone anticoagulation therapy may suffice if early recognition and treatment are feasible (31). Successful surgical intervention can result in favorable outcomes and recovery (32). In our case, we detected and confirmed the thrombosis during surgery using angiography. After three catheter-based aspirations, the majority of the thrombus was effectively cleared. Anticoagulant therapy was then initiated, and follow-up assessments indicated no thrombus-related risks or complications. Intraoperative vascular imaging showed severe narrowing in one area of the mesenteric veins after the thrombus was removed (Figure 1G). To prevent postoperative thrombus formation and secondary issues within the stent, we performed balloon dilation at the site of mesenteric venous stenosis. However, post-dilation imaging showed incomplete resolution of the stenosis problem. When the main portal vein or the upper mesenteric veins cannot be accessed during TIPS procedures, an extended stent should be used due to frequent blockages in the portal and splenic veins (15). It has been documented that extending stents to the distal SMV in TIPS procedures may jeopardize transplant surgeries(33). Therefore, the extension of TIPS stents to the SMV remains a topic of debate (34). In this case, we placed an uncovered stent at the distal end to ensure smooth blood flow through the narrowed segment of the mesenteric vein (Figure 1H). Contrast imaging showed effective blood flow through the TIPS channel into the heart, normalizing the portal pressure gradient. These results reinforce the introduction's insights on the efficacy of TIPS in managing portal hypertension despite complex challenges.

Postoperatively, the patient experienced occasional black stools, which were managed through the administration of acid-suppressing medications, fluid replacement, and the implementation of strict fasting policies. The black stools resolved, subsequent tests were negative for occult blood, and there was no notable drop in hemoglobin levels. Bleeding and potential mesenteric vein damage are risks following TIPS procedures. Patients with portal hypertension are more likely to experience these consequences due to their stronger vascular walls and higher portal vein pressure. Based on the patient's condition and the data we have collected, chronic liver disease is the primary cause of postoperative bleeding, while long-term portal hypertension and compromised vascular quality may contribute to the occurrence of black stools after surgery. In conclusion, our successful management of a complex case involving liver cancer, gastric varices, and portal venous cavernous transformation using a mesenteric approach for TIPS underscores the importance of selecting appropriate access routes and employing advanced imaging and thrombectomy techniques. This approach addresses major clinical challenges, improves patient prognosis, and highlights the reliability and efficacy of the mesenteric pathway for TIPS.

Preoperative imaging revealed abnormal perfusion in the liver. Computed tomography (CT) scans taken during the hepatic arterial phase showed high parenchymal enhancement in certain areas. These regions, known as transient hepatic attenuation differences (THADs) (35), appear as wedge-shaped zones with high blood flow during the hepatic arterial phase but become less dense in the venous and delayed phases (36). THADs can be associated with various conditions, including hepatocellular diseases, perihepatic diseases, portal vein obstructive diseases, liver tumors, hepatic inflammatory lesions, biliary tract diseases, and hepatic artery variations in the left hepatic lobe (37). In this case, the patient's abnormal hepatic perfusion was irregularly distributed in segments I, VI, and VII. The presence of localized abnormal perfusion changes warrants concern, as THADs may result from portal vein obstruction, potentially leading to temporary liver failure (35). The coexistence of malignant liver tumors and portal vein occlusion in this patient highlights the critical need to address these conditions. Diagnosis and treatment of liver diseases often involve identifying abnormal blood flow within the liver, and abnormal liver perfusion before surgery is commonly linked to PVT and HCC. Careful assessment of the patient's medical history and imaging results ruled out tumor spread to regions with irregular blood flow. The abnormal hepatic perfusion in this patient was attributed to PVT. TIPS placement has been shown to reduce portal pressures and improve systemic hemodynamics. However, issues with liver perfusion often remain unresolved (20, 38). Although significant improvements in abnormal perfusion were observed post-surgery, as evidenced by imaging (Figure 2C), ongoing monitoring is essential to ensure that no localized abnormal perfusion recurs. Follow-up examinations revealed notable enhancements in the patient's overall health and liver-kidney function, with no post-surgical complications and normalization of portal vein hemodynamic parameters. These findings provide valuable insights into managing complex cases requiring TIPS intervention.

The current TIPS program is advanced and sophisticated, allowing us to successfully complete a highly complex case and demonstrate our expertise in conducting TIPS procedures. Despite the positive outcome, this case certain limitations. The puncture of the mesenteric vein illustrates the technical challenges inherent to the procedure, necessitating precise surgical skills and advanced techniques. During the intervention, we encountered challenges, particularly with stent placement, but the patient's outcomes were favorable, underscoring the significance of experience. A holistic approach is essential in managing complex TIPS cases, with an emphasis on addressing complications and improving patient symptoms. These results validate our management strategy and emphasize the need for

TABLE 1 Levels of serum liver function, renal function, portal vein diameter, and flow velocity.

Group	AST (U/L)	ALT (U/L)	Cr (umol/L)	BUN (mmol/L)	Internal diameter (mm)	Velocity (cm/s)
Before surgery	125.08	93.06	37.47	7.61	5	-
One month after surgery	31.93	41.32	26.82	3.33	6.8	148
Two months after surgery	48.65	25.96	25.85	3.07	6.8	108

continuous improvement informed by new developments and successes.

The patient's favorable overall health status can be attributed to her insightful understanding of her medical condition, diligent adherence to prescribed treatments, and her occupation as a healthcare professional. Despite being diagnosed with malignant liver tumors, she exhibited a swift postoperative recovery. By the second day following the procedure, she demonstrated comfortable and pain-free mobility. She was discharged home after 2 weeks. A portal vein color Doppler ultrasound conducted one and a half months after the procedure revealed that the stent lumen was clear, with unrestricted blood flow and an average speed of 148 cm/s (2 January, 2024) (see Table 1). CT scans revealed stable stent placement, tumor stability, significant improvement in varices, and the disappearance of abdominal and pleural effusions. Effective atomic sequence images showed clear portal vein cavities (see Figures 2C–E), and the patient did not experience any bleeding or hepatic encephalopathy during follow-up care. She remains under regular follow-up care.

4 Conclusion

A complex case of liver cancer was described, involving gastric varices and portal venous cavernous transformation, previously treated with splenectomy in 2012. Preparing multiple surgical strategies can improve the success rate during the operation. Proficiency in various surgical techniques is important. In this case, the patient presented with portal vein occlusion and had undergone a splenectomy, along with poor vascular and tissue quality due to long-term liver disease. Conventional TIPS was not possible. Therefore, a modified access through TIPS using the mesenteric approach was used to achieve portal decompression. In complex cases, a detailed evaluation of the condition and proactive anticipation are necessary to handle complications effectively and prevent adverse events.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee, Gansu Provincial Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

GS: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Formal analysis, Methodology, Supervision. JW: Formal analysis, Investigation, Writing – review & editing. BZ: Formal analysis, Investigation, Writing – review & editing. NZ: Formal analysis, Investigation, Writing – review & editing.

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Conflict of 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.

Publisher's note

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Research advances in serum chitinase-3-like protein 1 in liver fibrosis

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While liver fibrosis remains a serious, progressive, chronic liver disease, and factors causing damage persist, liver fibrosis may develop into cirrhosis and liver cancer. However, short-term liver fibrosis is reversible. Therefore, an early diagnosis of liver fibrosis in the reversible transition phase is important for effective treatment of liver diseases. Chitinase-3-like protein 1 (CHI3L1), an inflammatory response factor that participates in various biological processes and is abundant in liver tissue, holds promise as a potential biomarker for liver diseases. Here, we aimed to review research developments regarding serum CHI3L1 in relation to the pathophysiology and diagnosis of liver fibrosis of various etiologies, providing a reference for the diagnosis, treatment, and prognosis of liver diseases.

KEYWORDS

biomarker, chitinase-3-like protein 1, liver fibrosis, non-alcoholic fatty liver disease, viral hepatitis

1 Introduction

Liver fibrosis, caused by etiological factors such as hepatitis viruses, non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), toxins, and alcohol consumption, is a key driver of various chronic liver diseases and cirrhosis and is strongly associated with the prognosis of chronic liver disease (1–3). Liver fibrosis is a wound-healing response against hepatocyte injury. During liver fibrosis, extracellular matrix (ECM; rich in collagen I and III) formation increases, and hepatic stellate cells (HSCs) gradually transform into myofibroblasts, ultimately leading to a reduction in hepatocytes and an accumulation of ECM and fibrillar collagen (4). Liver fibrosis is histologically reversible, whereas cirrhosis reversal is more challenging (5). Therefore, early diagnosis of liver fibrosis and effective treatment during its reversible period are crucial.

Histopathological assessment remains the gold standard for diagnosing liver fibrosis Histopathological assessment provides key findings for a definitive diagnosis, allowing for the measurement of inflammatory activity, the degree of fibrosis, and the determination of therapeutic efficacy. However, as an invasive test, a liver biopsy carries a risk of postoperative complications such as pain, bleeding, infection, and even death. It is a costly procedure and may not always be well tolerated by patients. Moreover, the scope of liver biopsy is further limited in terms of sampling and inter-observer errors, highlighting limitations in accurately diagnosing and periodically evaluating the degree of liver fibrosis. Non-invasive imaging techniques, including transient elastography (TE), ultrasound radiation force impulse imaging (ARFI), and magnetic resonance elastography (MRE), are frequently used as liver stiffness

measurement (LSM) tests. However, since the M-probe can only detect a depth of 2.5–6.5 cm below the hepatic pericardium, obese patients may not obtain sufficient signals. There are also limitations for patients with ascites around the liver because shear waves cannot propagate in fluid. Therefore, TE cannot be used in patients with ascites or obesity (6). In addition, its results vary according to the experience of the operator, and differentiating between progressive and significant hepatic fibrosis can be challenging. While the overall efficacy of MRE is superior to that of TE, there are currently no guidelines concerning diagnostic thresholds for liver fibrosis that incorporate MRE-related liver elasticity values. Moreover, MRE is not a substitute for liver biopsy.

Serologic indicators provide unique advantages as they are non-invasive, simple, and highly reproducible. In addition, compared to biopsy testing, these markers offer the added advantage of indicating the level of fibrotic changes occurring throughout the liver. Determining the extent of liver fibrosis sensitively and accurately is difficult using only a single index, and in recent years, many non-invasive diagnostic models have been developed to partially replace liver biopsy. Currently, the commonly used serological diagnostic models are four serum liver fibrosis markers, namely, amino-terminal pro-peptide of type III pro-collagen (PIIINP), collagen IV (CIV), laminin (LN), and hyaluronic acid; the fibrosis-4 (FIB-4) index (7); and the aspartate aminotransferase (ASP)-to-platelet ratio index (APRI) (8). FIB-4 and APRI reduce the need for a liver biopsy by approximately 30–40%. The 2015 World Health Organization (WHO) guidelines for the prevention and treatment of hepatitis B and the Chinese guidelines for the prevention and treatment of chronic hepatitis B (CHB) both recommend FIB-4 and APRI, for the assessment and diagnosis of liver fibrosis. However, the diagnostic value of FIB-4 and APRI is limited to patients with CHB and chronic hepatitis C (CHC), and the diagnostic value of these serological markers in determining intermediate stages of liver fibrosis, specifically in diagnosing liver fibrosis due to other causes, remains unclear (9) (Table 1). CHI3L1, a member of the chitosanase family, is highly expressed in liver tissues, can be secreted into the ECM of the liver, and is highly expressed in hepatic fibrosis. Therefore, by reviewing the recent developments in serum CHI3L1 research, that is, the role of CHI3L1 in the pathogenesis and diagnosis of liver fibrosis, caused by different etiologic factors, we aimed to determine reference values to aid in the diagnosis, treatment, and prognosis of liver diseases.

2 Overview of CHI3L1

2.1 CHI3L1 structure and receptors

CHI3L1, commonly known as the chitin protein, is a glycoprotein (with a molecular weight of approximately 40 kDa) expressed by the *CHI3L1* gene located on chromosome 1q31-q32.35. CHI3L1 belongs to the 18-glycosyl hydrolase family, and its polypeptide chain consists of 383 amino acids. It has been named YKL-40, and owing to the N-terminal three amino acids at the N-terminal end of the peptide chain are tyrosine (Y), lysine (K), and leucine (L). The 18-glycosyl hydrolase family mainly includes chitinases and chitinase-like proteins (CLPs). Chitinases are proteins with true chitin-degrading ability, while CHI3L1 belongs to the CLPs. Due to a mutation in the catalytic residue glutamate, CHI3L1 does not possess hydrolase activity; however, it still has a high affinity for chitosan, binds to a variety of receptors, and induces a wide range of cellular responses (22, 23). Currently identified CHI3L1 receptors include heparin, collagen, IL-13Rα2, transmembrane protein 219 (TMEM219), galectin-3, and cluster of differentiation 44 (CD44). CHI3L1 functions by binding to the receptors.

For example, CHI3L1binds to CD44 and activates the ERK and Akt pathways, as well as phosphorylates β-catenin, which promotes metastasis in gastric cancer (24). In addition, CHI3L1 modulates the glioma microenvironment by interacting with galectin-3, increasing tumor immunosuppression, and promoting macrophage M2 polarization, a process that is negatively regulated by galectin-3-binding proteins by competing with galectin-3 for binding to CHI3L1 (25).

2.2 Synthesis of CHI3L1

CHI3L1 is a highly evolutionarily conserved secreted protein, first discovered in 1992 by Johansen et al. in the cell culture of the human osteosarcoma cell line, MG63 (26). Immunofluorescence staining of liver specimens from patients with NAFLD revealed that CHI3L1 in liver tissue was mainly derived from macrophages. Studies have shown that CHI3L1 is also derived from a variety of cells, including neutrophils, fibroblasts, vascular smooth muscle cells, chondrocytes, HSCs, and tumor cells (27–29).

CHI3L1 synthesis and secretion are regulated by a variety of factors. Many cytokines such as IL-1β, IL-13, IL-6, and IFN-γ stimulate CHI3L1 expression, which in turn can regulate the expression of cytokines such as IL-6, IL-8, IL-12, IL-18, IFN-γ, and tumor necrosis factor (30). Non-coding RNAs such as miR-125-3p, miR-342-3p, and linc00963 regulate CHI3L1 through signaling pathways and play a key role in regulating inflammation-driven liver fibrosis (31–33). Sarma et al. (32) reported that CHI3L1 expression is regulated through the miRNA-449a/NOTCH1 axis and that stabilized p65 interacts with CCAAT/EBPα in the CHI3L1 promoter region to upregulate CHI3L1 expression in hepatitis C. Furthermore, factors such as aging, ECM changes, stress, and drugs also modulate CHI3L1 expression (34).

2.3 Biological functions of CHI3L1

CHI3L1 is closely related to cell proliferation, apoptosis, cell differentiation, and cell invasion and is involved in embryonic development, inflammation, tissue remodeling, angiogenesis, and tumor metastasis (Figure 1); however, studies targeting serum CHI3L1 levels are limited (35). Additionally, CHI3L1 is involved in innate immune system and ECM remodeling and is associated with chronic viral hepatitis, alcoholic hepatitis, NAFLD, and other chronic liver diseases, with a close association between the degree of liver fibrosis and ECM synthesis (14, 36–38).

2.3.1 CHI3L1 as an inflammatory factor

Infection and inflammation stimulate the production of CHI3L1, which plays a major role in tissue injury, inflammation, tissue repair, and remodeling responses. CHI3L1 expression is upregulated in inflammatory conditions such as ulcerative colitis, Crohn's disease, rheumatoid arthritis, osteoarthritis, and hepatic sclerosis, as well as in solid cancers (22, 39–41). CHI3L1plays a key role in microenvironmental

TABLE 1 Diagnostic value of serum markers for liver fibrosis.

Index	Parameters	Diseases (cases)		AUC	Sensitivity (%)	Specificity (%)	Negative predictive value (%)	Positive predictive value (%)	REF
CHI3L1		CHB	Monoinfected with HBV	0.97	95.20	89.70			(10)
			HBeAg-negative patients with CHB	0.818	80.00	71.05			(11)
			Significant fibrosis (≥F2)	0.728	59.1	75.6			(12)
		CHC		0.809	78	81			(13)
		NAFLD		0.7638	70	76.80			(14)
APRI	AST, PLT	CHB		0.688	55.20	85.70			(10)
		CHC		0.8	91	47			(8)
		NAFLD		0.77	18.30	96.10			(6)
		ALD		0.7	13.20	77.60			(15)
FIB-4	PLT, ALT, AST, age	CHB		0.7844	65.40	73.60			(16)
		NAFLD		0.85	84.40	68.50			(17)
		ALD		0.85	58	91			(18)
PP score	PLT, PIIINP	Early treatment stage for CHB	Advanced fibrosis ($F \geq 3$, 225 cases)	0.775					(9)
			Advanced fibrosis ($F \geq 4$, 117 cases)	0.803					
			Liver cirrhosis ($F \geq 5$, 29 cases)	0.803					
		Post-treatment CHB	Advanced fibrosis (F ≥ 3,137 cases)	0.632					
			Advanced fibrosis (F ≥ 4, 65 cases)	0.700					
			Liver cirrhosis (F ≥ 5, 21 cases)	0.743					
NIS4 score	miR-34a-5p, A2M, CHI3L1, HbA1c	Prevalence of at-risk NASH*	Pooled validation cohort ($n = 702$)	0.80	81.50	63.00	77.90		(19)
CAP	CHI3L1, AFP, PLT	CHB, 337 cases		0.805–0.819	71.60–81.30	70.00–79.89			(20)
YKL-40 model	CHI3L1, AST, HA, PLT	ALT<2x the ULN CHB	Training group, 307 cases	0.786	71.74	72.85	80.88	61.68	(21)
			Validation group (153 cases)	0.831	71.79	85.33	85.33	71.79	

AUC, area under curve; REF, references; CHB, chronic hepatitis B; CHC, chronic hepatitis C; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; ALD, alcoholic liver disease; ULN, upper limit of normal.
*At-risk NASH was defined as non-alcoholic fatty liver disease activity score 4 or more and liver fibrosis stage 2 or more.

remodeling in different diseases (42). Schoneveld et al. (43) retrospectively analyzed serum CHI3L1 levels in patients with coronavirus disease 2019 (COVID-19), chronic obstructive pulmonary disease, and unrelated interstitial lung disease and found that CHI3L1 upregulation in patients was strongly associated with the level of inflammation. De Lorenzo et al. (44) found that plasma CHI3L1 levels were elevated in patients with COVID-19 and that this elevation might contribute to a poor prognosis. The researchers also reported that although systemic inflammation had returned to baseline levels and plasma CHI3L1 levels decreased after 4 weeks of clinical remission in the

patients with COVID-19,CHI3L1 levels in individuals that recently presented with systemic inflammation were significantly higher than those in healthy controls. This suggests that even after systemic inflammation returns to baseline levels, the stimuli that maintain CHI3L1 production may still be present.

2.3.2 Immunosuppressive effects

CHI3L1 has immunosuppressive functions and has been identified as a new target for T-cell blockade (45, 46). CHI3L1 blocks T-cell infiltration by promoting neutrophil recruitment and neutrophil extracellular trap formation, and CHI3L1 targeting promotes antitumor immunity in various tumor types (47). For example, in glioblastoma, upregulation of cancer-intrinsic CHI3L1 signaling regulates the immunosuppressive microenvironment by reprogramming tumor-associated macrophages, leading to tumor progression (25). CHI3L1 deficiency accelerates stroke by enhancing neuroinflammation via reduced M2 macrophage polarization (48–50). NOD-like receptor protein 3 (NLRP3) mimics some of the hepatic features of NASH, and breast regression protein 39 (BRP39) plays a regulatory role in NLRP3-mediated hepatic inflammation and fibrosis in NLRP3 hyperfunctional mice. f BRP39 knockdown reduces hepatic inflammation and fibrosis and decreases infiltrating lipid-associated macrophages and neutrophils, two immune cells that play a key role in NASH progression (51). These findings suggest that CHI3L1 may be a novel target for the treatment of immune liver injury as well as for other T-cell-mediated diseases.

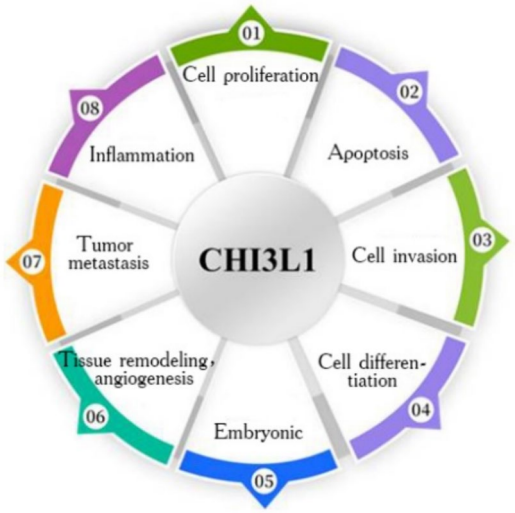

FIGURE 1
Biological functions of CHI3L1.

3 The relationship between CHI3L1 and liver fibrosis

Studies have shown that a variety of cells, including myofibroblasts, HSCs, hepatocytes, inflammatory cells, liver sinusoidal endothelial cells (LSECs), portal fibroblasts, and fibrocytes, are involved in liver fibrosis. Myofibroblasts are the main source of ECM in fibrotic liver and are not present in healthy liver tissues. Activated HSCs and portal fibroblasts transform into myofibroblasts during fibrosis, where HSCs play an important role in hepatic fibrosis. Quiescent HSCs reside in the defined space between LSECs and hepatocyte clusters (space of Disse). Upon activation, HSCs migrate to the site of injury and secrete ECM. CHI3L1 has been identified as a pro-fibrotic factor; it is overexpressed in aging livers and in patients with hepatic cirrhosis, thus given its key role in the development of hepatic fibrosis through direct action on HSCs and promotion of susceptibility to fibrosis in aging livers (34), CHI3L1 serves as a biomarker of hepatic fibrosis.

In a previous study involving 168 patients (non-hepatitis B, $n = 79$ patients; hepatitis B, $n = 89$ patients), we observed that in both patients with CHB and those without, there was a statistically significant difference in serum CHI3L1 levels between the significant and non-significant hepatic fibrosis group (Tables 2, 3; Supplementary material). It has been shown that in human and mouse fibrotic livers, CHI3L1 is mainly derived from hepatic macrophages and the accumulation of CHI3L1-positive hepatic macrophages is markedly enhanced during the fibrotic process, which may account for the elevated serum CHI3L1 levels (52). In a NASH mouse model, CHI3L1 regulated macrophage-hepatic stellate cell crosstalk, and direct stimulation of macrophages by CHI3L1 led to the upregulation of HSC-activating factor expression. In an *in vitro* study, stimulation of LX-2 cells with recombinant CHI3L1 showed direct activation of HSCs by

TABLE 2 Serum CHI3L1 levels in patients with CHB.

Patients with CHB	M (P25, P75)	Median difference (95% CI)	Wilcoxon two-sample rank sum test	
			Z-value	*p*-value
No significant liver fibrosis group ($n = 45$)	95.18 (68.39–112.38)	−73.489 (−87.320 to −59.509)	−7.476	<0.001
Significant liver fibrosis group ($n = 44$)	165.23 (141.11–192.65)			

TABLE 3 Serum CHI3L1 levels in patients with no hepatitis B.

Patients with no CHB	M (P25, P75)	Median difference (95% CI)	Wilcoxon two-sample rank sum test	
			Z-value	*p*-value
No significant liver fibrosis group ($n = 30$)	113.11 (97.56–118.60)	−8.153 (−16.069 to −0.453)	−2.101	0.036
Significant liver fibrosis group ($n = 49$)	118.49 (103.62–128.68)			

CHI3L1 through the receptor IL13Rα2, which led to the upregulation of pro-fibrotic factors in the liver (53). Recombinant CHI3L1 promotes the proliferation and activation of primary human HSCs (34).

CHI3L1 inhibits hepatic macrophage apoptosis by suppressing Fas expression and activating the Akt signaling pathway in an autocrine manner, leading to hepatic macrophage accumulation and activation, which exacerbates liver fibrosis. CHI3L1 inhibits apoptosis in M1-like but not M2-like hepatic macrophages (52). In conclusion, by inhibiting hepatic macrophage aggregation and promoting apoptosis, CHI3L1 deficiency could ameliorate hepatic fibrosis; thus,CHI3L1 can serve as a potential therapeutic target for liver fibrosis.

4 Application of CHI3L1 in the diagnosis of liver fibrosis

4.1 CHB

Hepatitis B virus (HBV) infection is a major global public health issue. WHO estimates that of the 296 million people chronically infected with HBV globally, nearly 820,000 died due to HBV-related diseases in 2019. Furthermore, in approximately 15–40% of untreated patients, HBV infection will progress to cirrhosis or hepatocellular carcinoma (HCC). As the world's most populous country, China has approximately 100 million HBsAg carriers (prevalence, 7.8%), and the annual number of deaths from HBV-related liver diseases is 162,000, accounting for approximately 29% of HBV-related deaths globally (54). China has made efforts to reduce the incidence of HBV infection over the past three decades (55), and aims to be a major contributor to the WHO's goal of "eliminating viral hepatitis as a major public health threat by 2030."

CHB is a dynamically progressive disease, and several clinical studies have shown that timely and effective antiviral therapy can slow or even reverse CHB-induced liver fibrosis (56, 57). The American Association for the Study of Liver Diseases and Asian Pacific Association for the Study of Liver Diseases guidelines recommend antiviral therapy for patients when the alanine transaminase (ALT) levels that are twice the upper limit of normal (ULN) levels (58, 59). However, in Chinese patients with CHB, ALT levels and the degree of fibrosis are not consistent, regardless of the HBe-Antigen (HBeAg) status and HBV DNA levels. Moreover, significant hepatic fibrosis has also been present in patients with CHB and an ALT level less than twice the ULN (21). Therefore, in the 2022 Expert Opinion on Expanding Antiviral Therapy for CHB, published by the Chinese Medical Association's Section of Hepatology, it was suggested that antiviral therapy be initiated when a non-invasive diagnosis suggests significant inflammation or fibrosis in the liver (60).

Serum CHI3L1is associated with a high diagnostic value in CHB-related liver fibrosis. In HBeAg-negative patients with CHB, serum CHI3L1 has high diagnostic efficiency in the staging of liver fibrosis, with a sensitivity and specificity of 80.00 and 71.05%, respectively (11). In patients with CHB and an ALT less than twice the ULN, serum CHI3L1 levels are independently associated with advanced liver fibrosis and serve as a potential biomarker for liver fibrosis. The study also constructed a model based on CHI3L1, which significantly outperformed the existing scores in patients with CHB having normal and mildly elevated diagnostic ALT levels (FIB-4, APRI, Huu Model, and Forns' index). This finding may guide clinicians in diagnostically identifying patients who may benefit from antiviral therapy (21).

Huang et al. (20) used univariate and multivariate logistic regression analyses to identify three independent predictors of advanced liver fibrosis in 337 patients with CHB (CHI3L1, AFP, and PLT indexes), and a new diagnostic model was established, namely, the CHI3L1/AFP/PLT (CAP) index. This index facilitated the diagnosis of advanced liver fibrosis with an AUROC significantly higher than that in the APRI and FIB-4, which is more suitable for patients with CHB. The diagnostic efficacy in advanced liver fibrosis is not affected by ALT level and HBeAg status, making it suitable for patients with CHB at different stages and helps in predicting the timing of antiviral therapy in these patients. A research team from Ningbo University examined the serum CHI3L1 expression in patients with CHB, liver cirrhosis, and HCC and investigated the expression characteristics of chronic liver diseases related to hepatitis B in different stages. The results of the investigation showed that the expression level of CHI3L1 progressively increased from CHB and liver cirrhosis to HCC, and the CHI3L1 expression offers clinical value in evaluating the different stages of chronic liver diseases and may be used as an indicator to monitor the disease evolution (10). However, other similar studies have suggested that CHI3L1 levels cannot significantly differentiate early liver fibrosis (meta-analysis of histologic data in viral hepatitis [METAVIR]F0, F1, and F2) (12).

CHI3L1 is a useful non-invasive marker for assessing liver fibrosis prior to treatment in patients with CHB and monitoring changes in liver fibrosis during treatment. Lin et al. (38) compared serum CHI3L1 levels, the hepatic tissue collagen proportional area (CPA), and LSM in 131 patients with CHB who received entecavir antiviral therapy for 78 weeks and found that serum CHI3L1 levels decreased from baseline after 78 weeks of treatment and were positively correlated with CPA and LSM.

In conclusion, the value of CHI3L1 expression in assessing significant liver fibrosis in patients with CHB is clearer and superior to currently known non-invasive diagnostic methods, and it serve as a reliable reference for antiviral therapy. However, as the diagnosis of early stage liver fibrosis is not highly accurate, a more appropriate non-invasive indicator for an individual or combined diagnosis remains to be identified.

4.2 CHC

Hepatitis C infection is a global epidemic trend, and people of different sexes, ages, and ethnicities are generally susceptible to HCV. According to the WHO, approximately 58 million people worldwide are currently infected with HCV, and approximately 290,000 deaths are attributed to HCV infection annually. In 2020, China had the largest number of HCV-infected individuals (approximately 9,487,000 people) (61). HCV infection is prone to chronicity, with approximately 55–85% of cases of acute hepatitis C developing into CHC. Cirrhosis and HCC are the main causes of death in patients with CHC (62). There is no effective vaccine to prevent HCV infection; however, as the treatment of hepatitis C enters a new era in terms of direct antiviral agents (DAAs), with an increasing number of patients achieving a sustained virologic response (SVR), post-treatment benefits and clinical outcomes are fast becoming the focus for future studies. The prognosis of patients after viral clearance is closely related to the degree of fibrosis (63), the early diagnosis of

HCV-associated hepatic fibrosis, and staging; thus, timely interventions are crucial.

Little is known concerning the progression of hepatic fibrosis after HCV eradication; however, recent studies have suggested that serum CHI3L1 levels may be a non-invasive marker for monitoring fibrosis in patients with CHC. Treatment with DAAs significantly and sustainably improved hepatic fibrosis in patients with CHC, with serum CHI3L1 levels being significantly lower at the end of treatment compared baseline levels (64–66). In one study involving 105 patients with CHC treated with DAAs, CHI3L1 was identified as a sensitive marker for monitoring changes in fibrosis during treatment and in the weeks after having reached an SVR. Early identification of treatment success at the end of treatment using CHI3LI levels may facilitate a timely shift to alternative treatments (64). Similar international studies have been conducted. Researchers at Helwan University studied the risk of HCC susceptibility in Egyptian patients with hepatitis C after SVR through DAA treatment and found that the *CHI3L1* gene (rs880633) could serve as a strong predictor and risk factor for patients to develop HCC post-SVR (67). While some studies have suggested that diagnosis using non-invasive indicators can be confounded by factors such as liver inflammation, a study from the First People's Hospital of Peking University concludes the utility of treatment with DAAs to achieve a rapid and significant reversal of hepatic fibrosis in addition to relieving inflammation and highlights that this regression can be detected as early as the end of therapy (66).

In summary, serum CHI3L1 levels are associated with the severity of fibrosis in CHC and its progression over time, which is clinically important for monitoring the degree of hepatic fibrosis and thus predicting the clinical outcome in patients with an SVR after treatment with DAAs. However, the benefits of CHI3L1 in the diagnosis of mild and severe fibrosis remain unclear.

4.3 Chronic hepatitis D

In recent years, there has been a renewed focus on hepatitis D virus (HDV) in several countries and regions, and comprehensive reports have shown that there are approximately 15–20 million cases of HDV infection worldwide, which is equivalent to approximately 5% of the chronically infected population with HBV (68). HDV is a defective RNA virus that requires the aid of HBV to complete its life cycle. Compared with HBV infection alone, overlapping HBV/HDV infections accelerate disease progression. It has been estimated that 70% of patients infected with HDV develop cirrhosis within 5–10 years and 60% succumb to disease within 10 years, in addition to a 28% increase in the risk of HCC in those infected with HBV/HDV (69, 70).

In the process of eliminating the viral hepatitis public health threat, it is important to emphasize and act in relation to chronic HBV, HCV, and HDV infection. With the application of nucleoside (acid) analogs and polyethylene glycol interferon-alpha, CHB can be effectively controlled, resulting in HBsAg-negativity and potential reversal of hepatic fibrosis, or even re-compensation after decompensation, can be achieved in some patients. Therefore, hepatitis D is emerging as a chronic viral hepatitis that cannot be neglected in the process of eliminating viral hepatitis-related public health hazards. At present, there are few studies on the use of CHI3L1 for the diagnosis of liver fibrosis due to HBV/HDV overlapping infections. One study in the United States (34) detected *CHI3L1* gene expression in the liver tissues of 64 patients with liver cirrhosis of different etiologies using quantitative reverse transcription polymerase chain reaction testing: CHI3L1 expression was significantly higher in the livers of patients with liver cirrhosis of various etiologies than in controls, with the highest in cirrhosis due to HDV, followed by HCV, HBV, and alcoholic cirrhosis. Interestingly, CHI3L1 was significantly higher in HDV than in HBV cirrhosis, despite HDV dependence on HBV. In the study, all patients with HDV-induced liver cirrhosis tested positive for serum HDV RNA and anti-HDV (IgG), with 82% of patients positive for anti-HDV (IgM). In addition, patients with HDV liver cirrhosis had the lowest platelet counts, consistent with typical splenomegaly, and the highest activity grading ($p < 0.001$) compared with alcohol-related cirrhosis and hepatitis C- and B-related diseases, reconfirming that hepatitis D is the most severe form of chronic viral hepatitis. In conclusion, chronic HDV infection is currently underappreciated and understudied in China, and the important role of CHI3L1 in chronic HDV progression and diagnosis needs to be further explored.

4.4 NAFLD

Currently, NAFLD is the most common chronic liver disease worldwide, with a prevalence rate of up to 25%. It is one of the leading causes of liver disease-related mortality (71). Characterized as excessive accumulation of liver fat, NAFLD is due to hepatic steatosis without excessive alcohol consumption and is a type of metabolic stress liver injury closely related to insulin resistance and genetic susceptibility, which mainly includes NASH, cirrhosis, and HCC. Approximately 20% of patients with NAFLD can progress to more severe NASH (72, 73), a severe type of NAFLD characterized pathologically by inflammation, hepatocellular injury, lipid degeneration, and fibrosis. With type 2 diabetes and obesity, NASH is increasingly becoming a public health concern, and, without clinical intervention, it can progress to severe liver diseases such as liver failure, cirrhosis, and HCC, potentially necessitating liver transplantation (72). Among various liver histologic indices, the liver fibrosis stage is an independent predictor of long-term prognosis in patients with NAFLD. Therefore, early identification of patients with NASH and significant fibrosis is crucial.

Integration of liver transcriptome datasets using the robust rank aggregation method to construct transcriptomic profiles of NASH progression and fibrosis severity in patients with NAFLD revealed that the *CHI3L1* gene was located in the top 10 upregulated genes in patients with NASH (74). One study suggests that CHI3L1 may be a potential marker for predicting significant fibrosis in patients with NAFLD (75). Kumagai et al. (14) measured serum CHI3L1 levels in 111 patients with NAFLD and 23 patients with HCC combined with NAFLD and found that serum CHI3L1 levels in patients with NAFLD increased with the progression of hepatic fibrosis. Additionally, CHI3L1 was significantly correlated with severe fibrosis (F3–4), and patients with HCC combined with NAFLD had significantly higher serum CHI3L1 levels than patients with NAFLD and non-HCC.

Harrison et al. (19) developed and externally validated a new blood-based non-invasive diagnostic model, namely, the NIS4 score, consisting of the following four metrics: miR-34a-5p, α-2 macroglobulin, CHI3L1, and glycated hemoglobin, specifically designed to identify patients with metabolic risk factors (type 2 diabetes mellitus, obesity, dyslipidemia, and hypertension) in patients with high-risk NASH (including those with an NAFLD activity

score ≥ 4 and fibrosis stage ≥2). This model offered improved NIS4 diagnostic performance and was not affected by age, sex, body mass index, or aminotransferase concentration. The study concluded that although the diagnostic efficacy of CHI3L1 alone was not significant, the NIS4 for high-risk NASH outperformed other blood-based diagnostic scores such as the FIB-4, the NAFLD fibrosis score(NFS), and APRI (NIS4, AUC = 0.80; CHI3L1, AUC = 0.69; APRI, AUC = 0.74; FIB-4, AUC = 0.70; NFS AUC = 0.66). The data also showed that while FIB-4 and NFS showed high specificity, their low sensitivities could lead to misleading diagnostic results for NASH, especially for the adjudication of high-risk NASH cases. In contrast, the sensitivity and specificity of NIS4 were optimally balanced. NFS mainly targets NAFLD-associated liver fibrosis; however, it is not a suitable screening indicator because it leads to overdiagnosis and high percentage of false negatives (76). The NIS4 model was further optimized in 2023 as the NIS2 + ™ (including miR-34a-5p and YKL-40), providing a more effective non-invasive method in which to rule out high-risk NASH for patients at risk (77).

Hepatic insulin resistance is known to have an important role in the development of NASH; however, the exact mechanism of action remains unclear. Zhang et al. (78) suggested that *CHI3L1* gene upregulation may be an important factor in the generation of the NAFLD/NASH phenotype. The researchers constructed a CHI3L1 knockout mouse model and observed improved insulin signaling in the CHI3L1 knockout mice compared with C57BL/6 wild-type (WT) mice fed the same diet, suggesting that decreasing the expression of CHI3L1 in the liver or inhibiting its function could ameliorate insulin resistance in the liver. To further confirm this finding, three anti-CHI3L1 monoclonal antibodies (FRG, CH568, and CHXI3B6) were used in the study. All three anti-CHI3L1 monoclonal antibody proteins inhibited their *in vivo* functions of CHI3L1 to varying degrees and significantly improved insulin resistance in the liver after 16 weeks of anti-CHI3L1 monoclonal antibody treatment. Additionally, although the CHI3L1 protein was expressed at different levels in the hepatocytes of patients with NAFLD and NASH, the positive cells of both were mainly localized in the hepatoportal vasculature, and immunohistochemical staining revealed abundantly expressed CHI3L1 in infiltrating inflammatory cells and hepatocytes. Overall, CHI3L1 is important for the diagnosis of advanced NAFLD-associated hepatic fibrosis and increased CHI3L1 expression directly correlates with hepatic fibrosis progression. CHI3L1 is expected to be a therapeutic target against monoclonal antibodies, but its role in the mechanism of hepatic fibrogenesis needs to be further investigated. Future studies are required to confirm the role of CHI3L1 in hepatic fibrosis (that is, determine whether CHI3L1 is a co-existing hepatic fibrosis factor or whether it promotes the formation of hepatic fibrosis).

4.5 Other liver diseases

In addition to viral hepatitis and NAFLD, excessive alcohol consumption and autoimmune liver disease can lead to serious negative outcomes. Among the different types of fatty liver diseases, the incidence of alcohol-related liver disease(ALD) related cirrhosis and HCC is the highest (79). However, the main cause of cirrhosis in China at this stage is still viral hepatitis. Although viral hepatitis is currently the primary cause of cirrhosis in China, the proportion of alcoholic cirrhosis has seen an increase in recent years. The epidemiologic study in China is still in the primary stage. The risk of HCC in autoimmune hepatitis is lower than that of other chronic liver diseases. A long-term follow-up study based on 1,428 patients with autoimmune hepatitis (AIH) found that only 1.7% of patients developed HCC with cirrhosis, only mildly increased the risk of HCC (80). Clinical and basic research on autoimmune liver disease in China has just begun, and there is a lack of relevant epidemiologic information, resulting in serious clinical underdiagnosis and mistreatment. In contrast, the evaluation of CHI3L1 in ALD as well as AIH-associated hepatic fibrosis has been reported less frequently, underscoring the need for further exploration of the important role of CHI3L1 in their progression and diagnosis.

5 Discussion

The destruction of hepatocytes owing to alcohol abuse, drugs, HBV, and autoimmune factors causes acute injury to the liver. Aseptic inflammation of the liver promotes the repair of liver damage and scar tissue proliferation, overaccumulation of the ECM, and the continuous proliferation of collagenous tissue. If injury factors persist in the liver, the injury can further progresses to hepatic fibrosis, which represents the early stage of a wide range of chronic liver diseases. Liver fibrosis, an early manifestation of various chronic liver diseases, can further develop into cirrhosis or HCC. Early diagnosis and intervention of liver fibrosis are expected to reverse its progression.

Liver tissue biopsy is currently the gold standard for the diagnosis of liver fibrosis; however, its widespread adoption is challenged by its several limitations, including invasiveness, low reproducibility, limitation of sampling, and subjectivity of diagnosis. Current non-invasive tests are mainly divided into imaging and serologic diagnostic models. The LSM detected by FibroScan-based TE can relatively accurately identify progressive liver fibrosis and early cirrhosis, but the measured value is affected by various factors such as liver inflammation and necrosis, cholestasis, and severe steatosis, and there is still a lack of a reliable diagnostic threshold. A serologic diagnosis is more easily accepted as it is more convenient and less influenced by human factors. Currently, the APRI and FIB-4 diagnostic models are acknowledged for their clear diagnostic value. However, both are derived from the data of patients with CHC, and although their diagnostic value in CHB is gradually recognized, the scope of application remains limited. Reliable diagnostic indexes for individual or combined testing have not been identified.

As a biological indicator related to inflammation, CHI3L1 is clinically important for the diagnosis and staging of liver fibrosis caused by various factors, especially for the diagnostic value of advanced liver fibrosis, and it can be used to determine the progression of liver fibrosis.

Serum CHI3L1 is an important diagnostic indicator for CHB liver fibrosis and is important in guiding antiviral therapy. Additionally, CHI3L1 may be associated with insulin resistance and obesity in the pathogenesis of NASH, and hepatic insulin sensitivity can be partially restored by parenteral given anti-Chi3L1 monotherapy (78). Therefore, the development of monoclonal antibody therapeutics targeting CHI3L1 is expected to slow down the progression of NAFLD. Some studies have been conducted or are currently ongoing to investigate the effects of therapy targeting CHI3L1(YKL-40) in the treatment of some medical diseases and various cancer diseases. For example,CHI3L1 inhibitors, including GM-CT-01 and ONO-7475, undergo clinical trials for the treatment of cancer (81). CHI3L1 is also

expected to be an independent prognostic factor for HCC. Additionally, significant advances have been made in understanding the pathogenesis of CHI3L1 in liver fibrosis. In hepatitis C, HCV induces and maintains the production of CHI3L1 in liver parenchymal cells by synergistically inducing the TNF-α and ROS-MAPKs pathways through the sustained activation of NF-κB.

As positive feedback, the CHI3L1 protein increases HCV replication and stimulates the release of pro-hepatic fibrotic cytokines and cellular activity in the liver parenchymal cells and HSCs (82). CHI3L1 induces the production of miRNA-449a dysregulation, which regulates CHI3L1 expression by inhibiting the upstream component of the Notch1/NF-κB transcriptional regulatory complex, thereby modulating inflammation. This dysregulation may ultimately lead to liver fibrosis (83).

Thus, CHI3L1 is a very important protein, both as a marker of disease and as a therapeutic target. However, the serum CHI3L1 level alone has little diagnostic value for early liver fibrosis and tends to increase with age. The cellular origin of CHI3L1 in the injured liver and its specific mechanism of action in hepatic fibrosis remain unclear, and more in-depth studies are needed to determine whether CHI3L1 can indeed be used as a therapeutic target.

Author contributions

XH: Conceptualization, Writing – original draft. WL: Writing – original draft. JL: Writing – review & editing. BW: Writing – original draft. XQ: Conceptualization, Writing – review & editing.

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Conflict of 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1372434/full#supplementary-material

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Metabolomics reveals altered metabolites in cirrhotic patients with severe portal hypertension in Tibetan population

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Background: Portal hypertension (PHT) presents a challenging issue of liver cirrhosis. This study aims to identify novel biomarkers for severe PHT (SPHT) and explore the pathophysiological mechanisms underlying PHT progression.

Methods: Twenty-three Tibetan cirrhotic patients who underwent hepatic venous pressure gradient (HVPG) measurement were included. Eleven patients had an HVPG between 5 mmHg and 15 mmHg (MPHT), while 12 had an HVPG ≥16 mmHg (SPHT). Peripheral sera were analyzed using liquid chromatograph-mass spectrometer for metabolomic assessment. An additional 14 patients were recruited for validation of metabolites.

Results: Seven hundred forty-five metabolites were detected and significant differences in metabolomics between MPHT and SPHT patients were observed. Employing a threshold of $p < 0.05$ and a variable importance in projection score >1, 153 differential metabolites were identified. A significant number of these metabolites were lipids and lipid-like molecules. Pisumionoside and N-decanoylglycine (N-DG) exhibited the highest area under the curve (AUC) values (0.947 and 0.9091, respectively). Additional differential metabolites with AUC >0.8 included 6-(4-ethyl-2-methoxyphenoxy)-3,4,5-trihydroxyoxane-2-carboxylic acid, sphinganine 1-phosphate, 4-hydroxytriazolam, 4,5-dihydroorotic acid, 6-hydroxy-1H-indole-3-acetamide, 7alpha-(thiomethyl)spironolactone, 6-deoxohomodolichosterone, glutaminylisoleucine, taurocholic acid 3-sulfate, and Phe Ser. Enzyme-linked immunosorbent assay further confirmed elevated levels of sphinganine 1-phosphate, N-DG, and serotonin in SPHT patients. Significant disruptions in linoleic acid, amino acid, sphingolipid metabolisms, and the citrate cycle were observed in SPHT patients.

Conclusion: Pisumionoside and N-DG are identified as promising biomarkers for SPHT. The progression of PHT may be associated with disturbances in lipid, linoleic acid, and amino acid metabolisms, as well as alterations in the citrate cycle.

KEYWORDS

Tibetan, liver cirrhosis, portal hypertension, metabolomics, biomarkers

Introduction

Liver cirrhosis presents the end stage of various kinds of chronic liver disease (CLD), characterized by the accumulation of extracellular matrix and distortion of hepatic vascular architecture (1). Globally, cirrhosis claims approximately one million lives annually (2). In China, it is estimated to affect 7 million (0.51%) of the population (3). Portal hypertension (PHT) is a major complication of cirrhosis (4). It is defined as increased pressure in the portal vein, typically identified by a hepatic venous pressure gradient (HVPG) exceeding 5 mmHg (5). The primary pathophysiological change in PHT is increased intrahepatic vascular resistance due to morphological changes within the liver. Factors such as reduced nitric oxide synthesis and increased portal blood flow further exacerbate PHT (6). Complications from PHT, including ascites, variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome, are significant causes of emergencies, readmissions, and deaths among cirrhotic patients (5). Thus, PHT presents a troublesome problem in clinical management and is associated with a poor prognosis. Accurate assessment and early intervention for cirrhotic patients at high risk of severe PHT are of great importance to improve patient outcomes and reduce mortality and morbidity. Monitoring the pressure of the portal vein is also essential for assessing the effectiveness of pharmacological treatments and guiding therapeutic decisions (6).

Currently, HVPG remains the gold standard for diagnosing PHT (7). It is also invaluable for risk stratification, selecting appropriate treatments, evaluating PHT progression, and assessing treatment efficacy (8, 9). However, HVPG is acquired through catheterization of the hepatic veins (10). The invasive, demanding, and expensive features of HVPG limit its clinical application and hinder its widespread adoption in most medical centers. Non-invasive methods to measure PHT include Doppler ultrasound, liver transient elastography, magnetic resonance imaging, computed tomography, et al. However, inaccuracy in assessing the severity of PHT, limited universality, high cost, time-consuming, and radiation also restrict their extensive use (11, 12). Therefore, there is a significant need for developing a novel, non-invasive, economical, accurate, specific, and sensitive marker for the detection of PHT. This would facilitate regular monitoring of portal vein pressure and long-term management of PHT patients. Metabolomics is the study of metabolites with low molecular weight (e.g., <1.5 kDa) found in cells, biofluids, and tissues (13). The metabolome information can provide specific quantitative traits related to health and disease. The non-invasiveness and convenience of metabolomics make it widely employed in biomarker discovery and mechanisms elucidating (14).

The Tibetan population, residing in high-altitude regions, experiences extreme cold, low oxygen, and high ultraviolet exposure. This leads to unique physiological and medical traits valuable for medical research (15). However, medical research on the population in this region remains limited due to factors such as remote geography, harsh environments, and cultural differences. Metabolomic analysis of liver diseases is also a gap in understanding. The present study aimed to describe the metabolic profile of Tibetan cirrhotic patients with PHT and identify the unique metabolites and potential mechanisms associated with PHT progression (defined as an HVPG ≥16 mmHg).

Materials and methods

Ethical consideration

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted following the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region (Research No. 64 of the Year 2020).

Inclusion and exclusion criteria

Inclusion criteria: Cirrhotic patients hospitalized between November 2020 and June 2023 at the Hospital of the Chengdu Office of the People's Government of the Tibetan Autonomous Region, which primarily provides medical services to the Tibetan population, were studied. Tibetan patients aged 18–75 years who met the diagnostic criteria for liver cirrhosis (16) and were going to undergo the HVPG measurement during their hospitalization were included. Tibetan ethnicity was confirmed by identification as Tibetan on a Resident Identity Card and long-term residency in the Tibetan Plateau.

Exclusion criteria: Pregnant or lactating women, patients with mental illnesses, or those with grade 2 or 3 hepatic encephalopathy were excluded.

A total of 23 patients were finally enrolled in the study. Based on HVPG, these patients were categorized into two groups: mild-to-moderate PHT (MPHT): 11 patients with an HPVG ranging from 5 mmHg to 15 mmHg; severe PHT (SPHT): 12 patients with an HPVG of 16 mmHg or higher. An additional cohort of 14 patients was included for the validation, adhering to the same inclusion and exclusion criteria. These patients were divided into two groups: validation-MPHT (VMPHT): 6 patients with an HPVG ranging from 5 mmHg to 15 mmHg; validation-SPHT (VSPHT): 8 patients with an HPVG of 16 mmHg or higher.

Metabonomic analysis

Serum extraction: Peripheral blood samples were collected from the cirrhotic patients using serum-separator tubes without anticoagulants. The collected blood was allowed to clot at room temperature for 30 min to 1 h, avoiding any vibration or movement of the tubes. Following clotting, the samples were centrifuged at 4°C and 3,000 rpm for 15 min. The supernatant serum was carefully aspirated and aliquoted into sterile Eppendorf tubes. The serum samples were immediately stored at −80°C. Transportation was carried out on dry ice. All samples were analyzed under the same experimental conditions.

Metabonomic analysis: The serum underwent a liquid chromatograph-mass spectrometer (LC-MS) for further metabonomic analysis. In short, the samples were separated by liquid chromatography, and then the single component entered the ion source of the high vacuum mass spectrometer for ionization. The mass spectrum was obtained according to the separated mass-to-charge ratio (m/z). Denoising smoothing, baseline correction, and overlapping peak identification were applied to extract the information of metabolites. Finally, the qualitative and quantitative results of the

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TABLE 1 Clinical characteristics of cirrhotic patients.

	MPHT (n = 11)	SPHT (n = 12)
Average HVPG (mmHg)	11.45 ± 2.07	20.92 ± 3.80
Male (n, %)	6 (54.55%)	6 (50%)
BMI	27.04 ± 3.70	25.37 ± 3.77
Mean age (years)	54.78 ± 5.64	54.58 ± 9.25
Varices (n)	9 (N = 10)	10 (N = 11)
Variceal bleeding (n, %)	5 (45%)	5 (41.67%)
Ascites (n, %)	7 (63.64%)	9 (75%)
Hepatic encephalopathy (n, %)	0 (0)	1 (8.33%)
Laboratory tests		
ALT (IU/L)	52.18 ± 43.58	38.83 ± 31.92
AST (IU/L)	52.27 ± 46.93	48.00 ± 33.65
ALB (g/L)	33.90 ± 6.43	33.90 ± 7.60
Tbil (μmol/L)	28.08 ± 14.87	28.37 ± 22.12
Hb (g/L)	109.55 ± 20.42	118.50 ± 33.92
PLT ($\times 10^9$/L)	71.27 ± 21.14	91.83 ± 32.65
Crea (μmol/L)	57.09 ± 7.53	84.25 ± 48.85
TC (mmol/L)	3.55 ± 0.92	2.95 ± 0.69
Triglycerides (mmol/L)	0.84 ± 0.22	0.73 ± 0.22
LDL (mmol/L)	2.14 ± 0.86	1.71 ± 0.56
FPG (mmol/L)	6.15 ± 3.04	5.11 ± 1.50
Child-pugh (n)		
A	2	4
B	7	6
C	2	2
Etiology (n)		
Hepatitis B	6	8
ALD	5	2
AIH	0	1
Cryptogenic	0	1

MPHT, mild-to-moderate portal hypertension; SPHT, severe portal hypertension; HVPG, hepatic venous pressure gradient; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; Tbil, total bilirubin; Hb, hemoglobin; PLT, platelet; Crea, creatinine; TC, total cholesterol; LDL, low-density lipoprotein; FPG, fasting plasma glucose; ALD, alcoholic liver disease; AIH, autoimmune hepatitis.

samples were obtained by normalizing, data transforming, and standardizing the mass spectrum data.

Validation of the differential metabolites

Serum levels of serotonin, sphinganine 1-phosphate (S1P), and N-decanoylglycine (N-DG) were measured using enzyme-linked immunosorbent assay (ELISA) kits from Jingmei Biotechnology. The assays were performed according to the manufacturer's instructions. Optical density at 450 nm (OD_{450}) was measured with a microplate reader, and the concentrations of the biomarkers were calculated using the standard curves provided with the kits.

Data analysis

Continuous variables were presented as mean ± standard deviation (SD). For comparing means between two groups with equal variances, the student's t-test was utilized. Conversely, when comparing means between two groups with unequal variances, Welch's t-test was employed. A p-value of less than 0.05 was considered statistically significant. Principal component analysis (PCA) and partial least squares-discriminant analysis (PLS-DA) were used to overview the metabolic profile of the MPHT and SPHT groups. The PLS-DA models were evaluated based on R2X, R2Y, and Q2 as indicators of their quality. R2X and R2Y signify cumulative explanatory rates, with Q2 reflecting the model's predictive capacity. Variable influence on projection (VIP) was obtained based on the orthogonal partial least square discriminant analysis (OPLS-DA) models. The differential metabolites were identified based on a combination of p-value and VIP. Metabolites were classified as differential if they met the criteria of $p < 0.05$ and VIP >1. Furthermore, metabolites that additionally exhibited a fold change (FC) greater than 1.2 under these conditions were categorized as significant differential metabolites. These analyses were conducted using the Majorbio Cloud Platform.[1]

Results

Characteristics of cirrhotic patients

A total of 23 cirrhotic patients who underwent HVPG were enrolled in the present study. Based on HVPG, the patients were divided into the MPHT group (n = 11) and the SPHT group (n = 12). The average HVPG of the MPHT group was 11.45 ± 2.07 mmHg, while it was 20.92 ± 3.8 mmHg in the SPHT group ($p < 0.001$). The main characteristics of the patients were summarized in Table 1. No significant differences were observed in the age, body mass index (BMI), and laboratory tests between the two groups.

Metabolic profile of peripheral serum from cirrhotic patients

A total of 745 metabolites (459 in positive ion mode and 286 in negative ion mode) were successfully identified. Among the metabolites, 593 were documented in the library. The termed metabolites were classified into 9 categories according to the Kyoto Encyclopedia of Genes and Genomes (KEGG) compound database. Phospholipids (26 metabolites), amino acids (11 metabolites), and carboxylic acids (8 metabolites) accounted for the most common categories (Figure 1A). The amino acid metabolism and lipid metabolism were the most frequent pathways that the metabolites were involved in Figure 1B. The top 20 KEGG pathways were shown in Figure 1C. The ATP-binding cassette (ABC) transporters, central carbon metabolism in cancer, bile secretion, and tryptophan metabolism presented the top four pathways.

PCA was applied to overview the metabolic differences between the MPHT and SPHT groups. A combination of overlapping and

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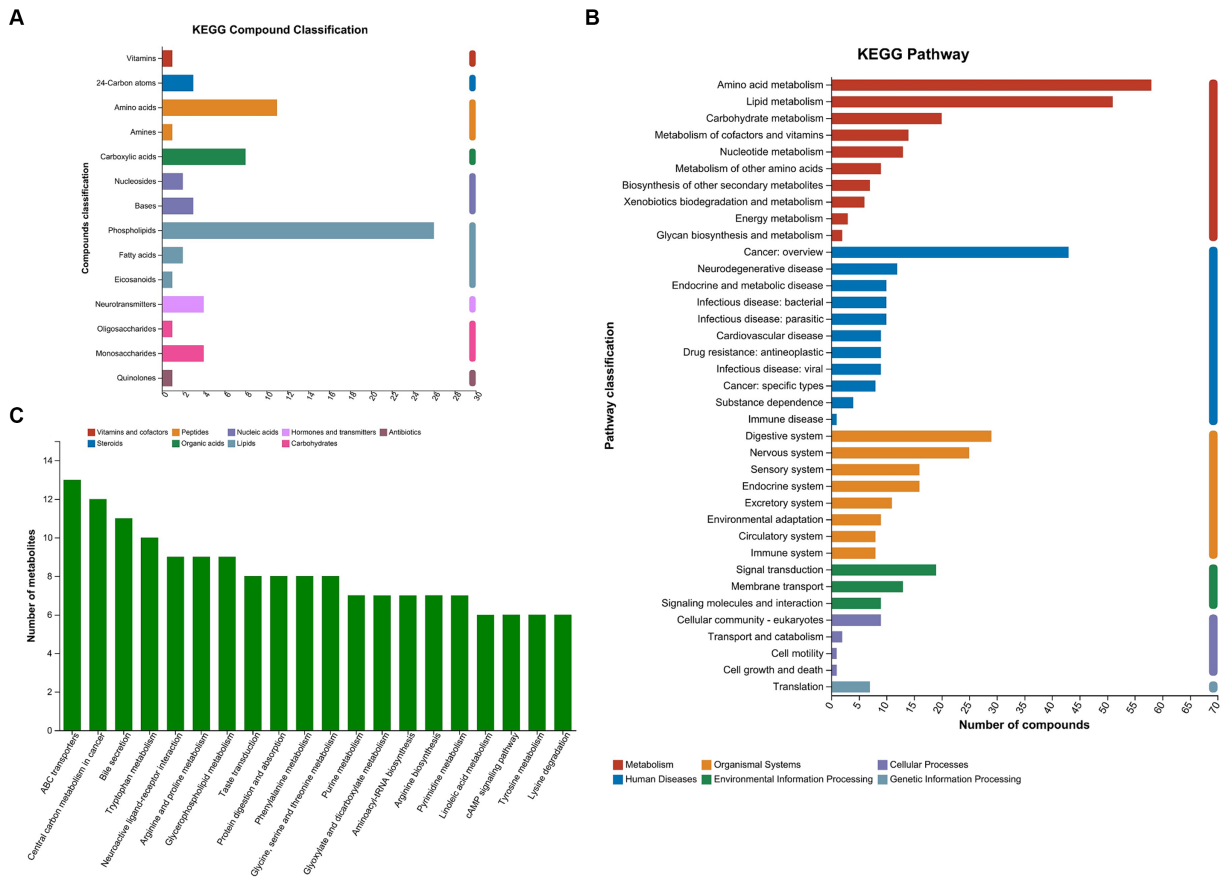

FIGURE 1
KEGG compound classification and KEGG pathways of the metabolites. **(A)** Metabolites were classified into 9 categories according to KEGG compound database. **(B)** The metabolites were annotated into KEGG pathways. **(C)** Top 20 KEGG pathways. KEGG, Kyoto Encyclopedia of Genes and Genomes; MPHT, mild-to-moderate portal hypertension; SPHT, severe portal hypertension.

distinct components between the two groups was observed in PCA (Figures 2A,B). Considering this unsupervised analysis may miss the discrepancy between groups, PLS-DA was employed to identify the differences in metabolic profile. As shown in Figures 2C,D, the metabolic profiles of serum from the two groups in the positive and negative ion modes were separated, indicating the unique metabolic profile of severe PHT patients. The clustered quality control (QC) samples indicated the system's stability and quality of the data. No outliers are present, and all values reside within the 95% confidence interval. Permutation testing showed the intercepts of Q2 = 0.831, R2X = 0.591, R2Y = 0.979 from the positive ion mode data and Q2 = 0.822, R2X = 0.536, R2Y = 0.98 from the negative ion mode data, indicating the model's stability, reliability, and robust explanatory and predictive capabilities. Furthermore, the intercepts of the Q2 regression lines with the *Y*-axis, in both positive and negative modes, were below 0.05, affirming the absence of model overfitting (data not shown).

Unique metabolites of SPHT

The differential metabolites were selected based on criteria including $p < 0.05$ and VIP >1, leading to the identification of 153 differential metabolites (89 in positive ion mode and 64 in negative ion mode). The discrepancies in metabolite profiles between the two groups were illustrated in volcano plots (Figure 3A). Notably, most of these metabolites were significantly elevated in the SPHT group. Applying stricter criteria of $p < 0.05$, VIP >1, and FC >1.2, only 17 significant differential metabolites were identified, with 15 being significantly upregulated in the SPHT group (Figure 3B and Table 2). Annotation of these metabolites in the Human Metabolome Database (HMDB) revealed that they predominantly belong to the superclass of lipids and lipid-like molecules and the class of carboxylic acids and derivatives.

The result of VIP analysis of the top 30 differential metabolites was shown in Figure 3C. Pisumionoside exhibited the most pronounced distinction between the two groups with the highest VIP and FC values (VIP = 5.58, FC = 3.77, $p < 0.001$). When annotated in the HMDB, a substantial proportion of the differential metabolites fell within the superclass of lipids and lipid-like molecules. This included pisumionoside, S1P, tsugaric acid B, 20-hydroxy-E4-neuroprostane, canrenone, taurodeoxycholic acid, taurochenodeoxycholate-7-sulfate, 6-deoxohomodolichosterone, taurocholic acid, 3-oxo-4,6-choladienoic acid, and alpha-calacorene. At the class level, N-DG, glutaminylisoleucine, and 4,5-dihydroorotic acid were categorized as carboxylic acids and derivatives. And 6-hydroxy-1H-indole-3-acetamide, L-4-chlorotryptophan, and serotonin were annotated to the class of indoles and derivatives.

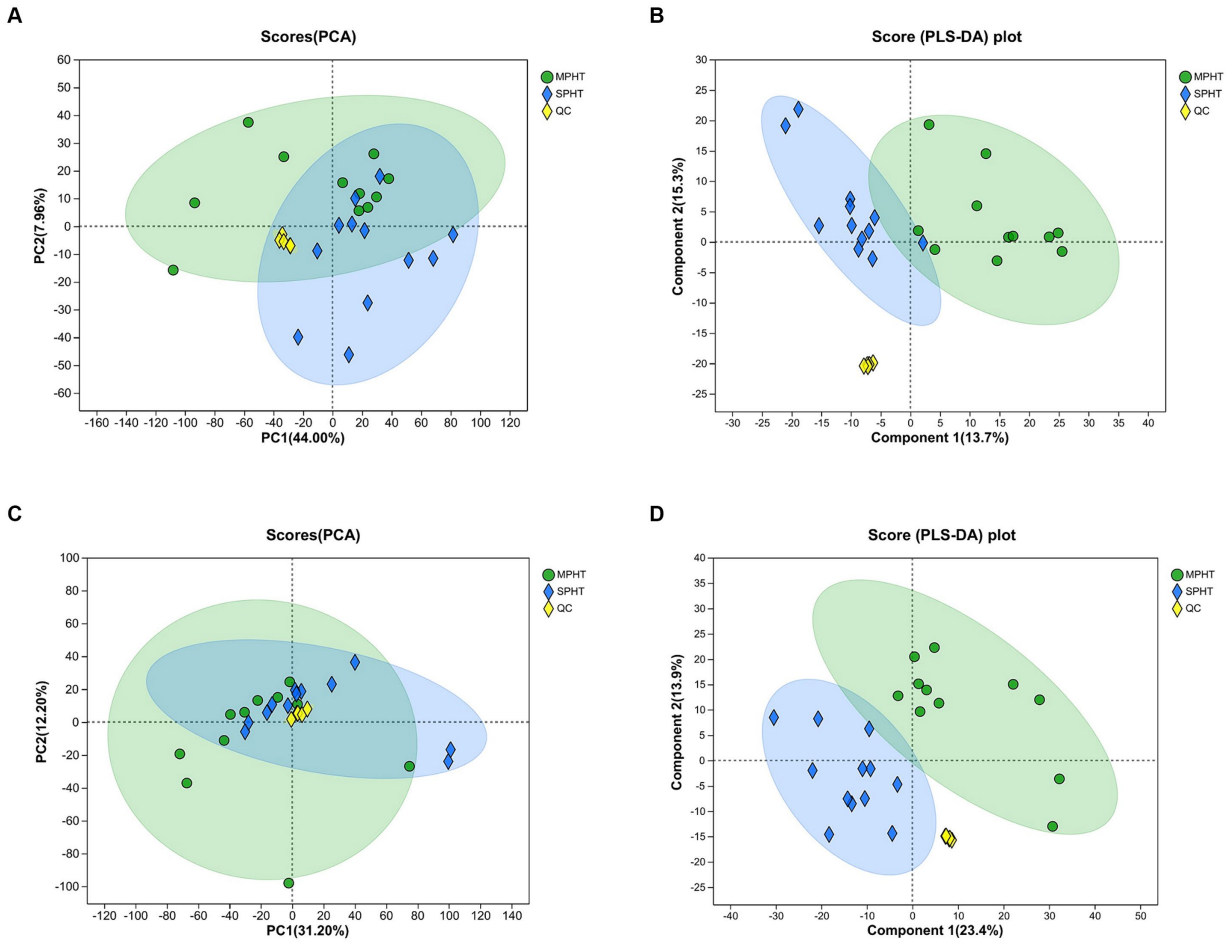

FIGURE 2
PCA and PLS-DA demonstrate the metabolic differences between the two groups. **(A,B)** PCA score plots between MPHT and SPHT groups in positive ion model **(A)** and negative ion model **(B)**. **(C,D)** PLS-DA score plots between MPHT and SPHT groups in positive ion model **(C)** and negative ion model **(D)**. PCA, principle component analysis; PLS-DA, partial least squares discriminant analysis; MPHT, mild-to-moderate portal hypertension; SPHT, severe portal hypertension.

Subsequent correlation analyses between primary clinical data and selected differential metabolites were performed (Figure 3D). Overall, blood lipids exhibited some correlation with the differential metabolites. Conversely, age, creatinine (Crea), total bilirubin (Tbil), aspartate aminotransferase (AST), albumin (ALB), and hemoglobin (Hb) did not show significant correlations. Specifically, pisumionoside demonstrated a negative correlation with body mass index (BMI), fasting plasma glucose (FPG), total cholesterol (TC), and triglycerides (TG). The metabolite 4-hydroxytriazolam showed a positive correlation with platelet count (PLT) and negative correlations with FPG, TC, and low-density lipoprotein (LDL). Metabolites related to the citrate cycle (TCA cycle) (citric acid, malic acid, and isocitrate) were found to be negatively correlated with blood lipids. Metabolites involved in tryptophan metabolism (serotonin, 5-hydroxyindoleacetylglycine, 3-hydroxyanthranilic acid, and 5-hydroxy-L-tryptophan) were correlated with alanine aminotransferase (ALT), PLT, blood lipids, and FPG, with serotonin showing positive correlations with ALT and PLT. N-decanoylglycine (N-DG), S1P, and linoleic acid metabolites (13(S)-HpODE, linoleic acid and 13-OxoODE) did not exhibit noticeable correlations with the clinical indicators.

Enrichment and clustering of differential metabolites

When annotated to the KEGG compound library, a total of 35 differential metabolites were identified. Among these, the majority, totaling 18, were classified under compounds with biological roles, followed by 12 metabolites categorized as lipids. Phytochemical compounds and pesticides had 4 and 1 annotated metabolites, respectively. No metabolites were annotated to endocrine disrupting compounds and bioactive peptides. In terms of secondary classification, amino acids (compounds with biological roles: L-methionine, trans-4-hydroxy-L-proline, N-formylmethionine, L-tyrosine, citrulline, and L-glutamine), carboxylic acids (compounds with biological roles: citric acid, 4-hydroxybutyric acid, isocitrate and malic acid), and ST05 Steroid conjugates (lipids: taurodeoxycholic acid, glycocholic acid, taurocholic acid) had the highest number of annotated differential metabolites. The top 30 differential metabolites annotated to the KEGG compound library revealed that the majority of differential metabolites belong to lipids (5 metabolites).

Upon alignment with the KEGG pathway database, the 17 differential metabolites exhibited enrichment in 20 pathways

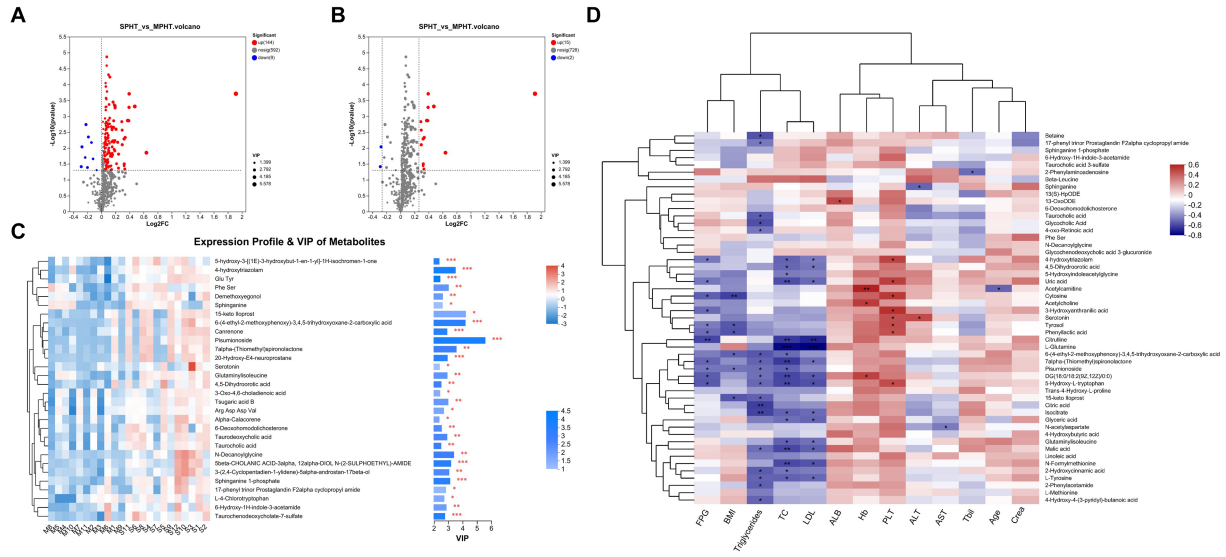

FIGURE 3
The differential metabolites between the MPHT and SPHT groups. **(A,B)** Volcano plots based on the OPLS-DA models. The differential metabolites were identified by the criteria of $p < 0.05$ and VIP >1 **(A)**, and $p < 0.05$, VIP >1 and FC >1.2 **(B)**. **(C)** Expression profile and VIP of the top 30 upregulated metabolites in SPHT patients. **(D)**The correlation heatmap of the clinical data and the differential metabolites. MPHT, mild-to-moderate portal hypertension; SPHT, severe portal hypertension; OPLS-DA, orthogonal partial least squares discriminant analysis; VIP, variable importance in projection; FC, fold change; FPG, fasting plasma glucose; BMI, body mass index; TC, total cholesterol; LDL, low-density lipoprotein; ALB, albumin; Hb, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Tbil, total bilirubin; Crea, creatinine.

(Figure 4A). The central carbon metabolism (CCM) pathway exhibited the most significant enrichment of differential metabolites, and it contains the highest number of such metabolites (6 metabolites). CCM includes glycolysis, the TCA cycle, and the pentose phosphate pathway. It is the most fundamental metabolic process, providing energy and metabolic precursors for the body (17). The enrichment of differential metabolites in the bile secretion pathway was also significant (6 metabolites). Additionally, the glyoxylate and dicarboxylate metabolism, taste transduction, phenylalanine metabolism, and tryptophan metabolism pathways all presented significant enrichment of differential metabolites. The KEGG enrichment analysis of the top 30 differential metabolites revealed that the pathways most significantly involved were the sphingolipid metabolism and the neuroactive ligand-receptor interaction pathway, where serotonin and S1P participated (data not shown).

KEGG pathway enrichment analysis showed that the differential metabolites were significantly enriched in the following pathways: Glyoxylate and dicarboxylate metabolism (impact factor 0.00), TCA cycle (impact factor 0.17), alanine, aspartate, and glutamate metabolism (impact factor 0.19), linoleic acid metabolism (impact factor 0.75), tryptophan metabolism (impact factor 0.21), and sphingolipid metabolism (impact factor 0.17) (Figure 4B). The impact factor denotes the relative importance of metabolites within each pathway. Network diagrams presented in Figure 4C and Figure 4D illustrated the positions of differential metabolites within the tryptophan and sphingolipid metabolism pathways. In Figure 4C, the compound C00630 refers to 5-Hydroxy-L-tryptophan, C00780 is identified as serotonin, and C00632 corresponds to 3-Hydroxyanthranilic acid. In Figure 4D, C00836 is sphinganine and C01120 represents S1P.

Identification of the potential biomarkers for SPHT

To assess the diagnostic capability of differential metabolites for SPHT, we conducted a receiver operating characteristic (ROC) curve analysis on the 15 significantly elevated differential metabolites in SPHT patients. The following differential metabolites presented area under the curve (AUC) >0.8 through ROC analysis: pisumionoside (0.947), N-DG (0.9091), 6-(4-ethyl-2-methoxyphenoxy)-3,4,5-trihydroxyoxane-2-carboxylic acid (0.8864), S1P (0.8712), 4-hydroxytriazolam (0.8636), 4,5-dihydroorotic acid (0.8561), 6-hydroxy-1H-indole-3-acetamide (0.8561), 7alpha-(thiomethyl)spironolactone (0.8561), 6-deoxohomodolichosterone (0.8485), glutaminylisoleucine (0.8409), taurocholic acid 3-sulfate (0.8258) and Phe Ser (0.8182) (Figure 5A).

As two differential metabolites with an AUC greater than 0.9, pisumionoside and N-DG also exhibited high VIP values and significant *p*-values, underscoring their potential as biomarkers for SPHT. Additionally, S1P demonstrated not only a significant difference in levels between the two groups but also its involvement in sphingolipid metabolism and the neuroactive ligand-receptor interaction pathways. Sphingolipid metabolism is crucial for the integrity of cell membranes, apoptosis, proliferation, and aging. The catabolism of sphingolipids generates ceramide and sphingosine, which are ultimately degraded into S1P (18). Then S1P works as a signaling lipid that regulates many cellular processes (19). The neuroactive ligand-receptor interaction pathway encompasses a group of receptors and ligands located on the plasma membrane and involves in various signaling processes (20). These suggested the significant role of S1P in the progression of PHT. To further validate whether these significant different metabolites were elevated in SPHT patients, we conducted ELISA on the relevant metabolites in the validation group. The results showed that N-DG and

TABLE 2 The significant differential metabolites upregulated in the SPHT patients.

Metabolite	Library ID	HMDB Superclass	HMDB Class	VIP	FC	*p*-value
Pisumionoside	HMDB0039947	Lipids and lipid-like molecules	Prenol lipids	5.5777	3.7703	0.000196
15-keto iloprost	—	—	—	4.208	1.5583	0.01402
6-(4-ethyl-2-methoxyphenoxy)-3,4,5-trihydroxyoxane-2-carboxylic acid	—	—	—	4.191	1.389	0.000491
7alpha-(thiomethyl)spironolactone	—	—	—	3.5642	1.2948	0.001363
4-hydroxytriazolam	HMDB0061052	Organoheterocyclic compounds	Benzodiazepines	3.4919	1.3141	0.000197
N-decanoylglycine	HMDB0013267	Organic acids and derivatives	Carboxylic acids and derivatives	3.3855	1.3069	0.001375
Sphinganine 1-phosphate	HMDB0001383; HMDB0242462; 19,794–97-9	Lipids and lipid-like molecules	Sphingolipids	3.1129	1.3125	0.000525
Phe Ser	—	—	—	3.0076	1.2497	0.005162
Glutaminylisoleucine	HMDB0028800	Organic acids and derivatives	Carboxylic acids and derivatives	2.9307	1.2634	0.004651
6-hydroxy-1H-indole-3-acetamide	HMDB0031173	Organoheterocyclic compounds	Indoles and derivatives	2.8637	1.2271	0.007869
17-phenyl trinor prostaglandin F2alpha cyclopropyl amide	—	—	—	2.8281	1.2519	0.03163
6-deoxohomodolichosterone	HMDB0034430	Lipids and lipid-like molecules	Steroids and steroid derivatives	2.5361	1.2266	0.002732
4,5-dihydroorotic acid	HMDB0003349; HMDB0000528	Organic acids and derivatives	Carboxylic acids and derivatives	2.5085	1.222	0.001479
Serotonin	50–67-9; HMDB0000259	Organoheterocyclic compounds	Indoles and derivatives	2.3852	1.2589	0.04574
Taurocholic acid 3-sulfate	HMDB0002581; LMST05020031	Lipids and lipid-like molecules	Steroids and steroid derivatives	2.0362	1.2496	0.03614

SPHT, severe portal hypertension; VIP, variable importance in projection; FC, fold change (SPHT/MPHT).

S1P were significantly higher in VSPHT patients compared to VMPHT patients ($p < 0.05$) (Figure 5B). The clinical information of the validation patients was listed in Supplementary Tables S2, S3. Except for HVPG, there were no significant differences in age, BMI, or laboratory test results between the two groups.

Although the AUC value of serotonin was less than 0.8, its involvement in various vital physiological processes, such as bile secretion, tryptophan metabolism, neuroactive ligand-receptor interaction, and taste transduction, suggested a close association with the development and progression of PHT. Therefore, we also verified its levels using ELISA. The result showed that serum serotonin in VSPHT patients was significantly higher than in VMPHT patients ($p < 0.05$), consistent with our metabolomic analysis.

Discussion

PHT represents a significant pathological alteration associated with cirrhosis, closely linked to severe complications and a poor prognosis in affected individuals. It has been documented that an HVPG exceeding 16 mmHg independently predicts mortality in cirrhotic patients, with values of 20 mmHg or higher indicating an extremely high risk of death (21). Therefore, measuring PHT is critical for identifying patients at high risk of complications and mortality, as well as for assessing responses to pharmacological treatment. Although HVPG is a highly accurate method for evaluating PHT, its invasive nature and technical demands limit its widespread application. Other non-invasive diagnostic methods for PHT include liver elastography, spleen elastography, and serum biomarkers (22). The high demands on equipment and operators for liver and spleen elastography, along with its accuracy being easily affected by obesity, limit its widespread application (23). Serum biomarkers offer high applicability, good reproducibility, and strong availability, making them highly promising for the non-invasive detection of PHT. Currently, available serum biomarkers include PLT count, Von Willebrand factor antigen, AST to PLT ratio index, AST-to-ALT ratio, Fibrosis-4 index, FibroIndex, and King's score, et al. (22). However, these biomarkers can be influenced by comorbidities or medications. Furthermore, many of these biomarkers are primarily used to assess liver fibrosis, and their accuracy in diagnosing PHT is limited, particularly when used alone. Though other biomarkers such as

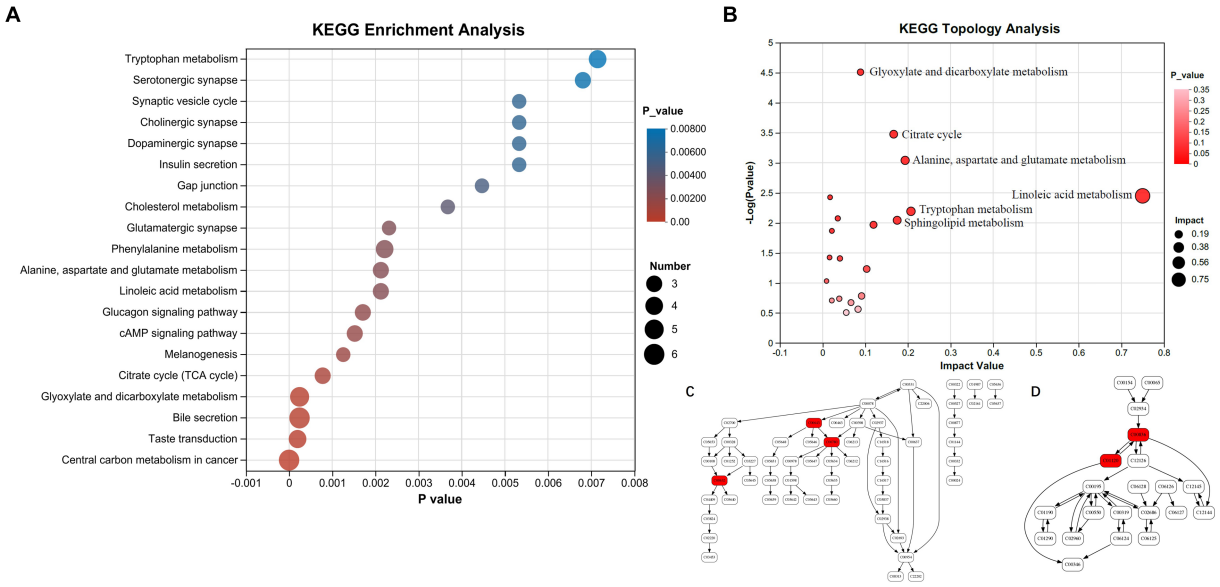

FIGURE 4
Enrichment analysis of differential metabolites in KEGG pathways. **(A)** KEGG pathway enrichment analysis. **(B)** Metabolic topology analysis. **(C)** Tryptophan metabolism pathway (serotonin, 5-hydroxy-L-tryptophan and 3-hydroxyanthranilic acid marked with red are significantly changed in peripheral blood plasma of SPHT patients). **(D)** Sphingolipid metabolism pathway (sphinganine and sphinganine 1-phosphate marked with red are significantly changed in peripheral blood plasma of SPHT patients). KEGG, Kyoto Encyclopedia of Genes and Genomes; MPHT, mild-to-moderate portal hypertension; SPHT, severe portal hypertension.

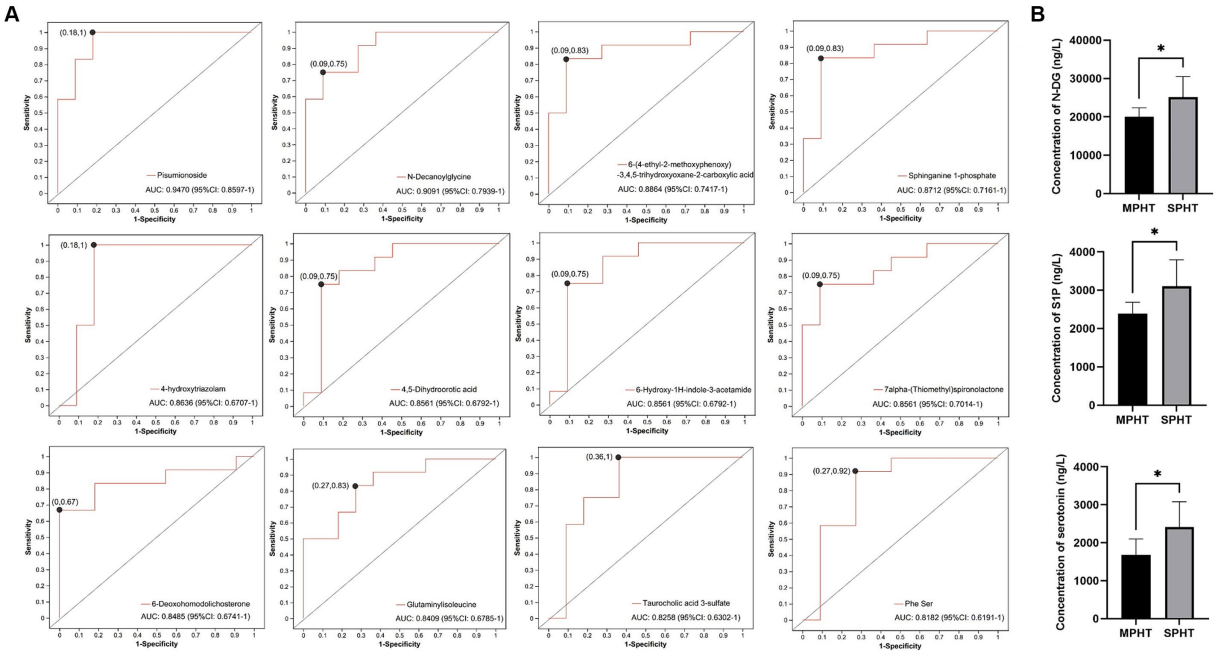

FIGURE 5
ROC curve analysis and ELISA validation of the significant differential metabolites. **(A)** ROC curves of the significant differential metabolites which have an AUC >0.8. **(B)** The serum concentrations of N-DG, S1P and serotonin using ELISA kits. *$p < 0.05$. ROC, receiver operating characteristic; AUC, area under the curve; ELISA, enzyme-linked immunosorbent assay; N-DG, N-decanoylglycine; S1P, sphinganine 1-phosphate.

soluble cluster of differentiation 163 (CD163) (24), inflammatory markers (25), and serum bile acids (26) have been investigated, current evidence is insufficient to recommend their routine use in clinical practice. Moreover, most existing biomarkers are primarily used to identify PHT with portal pressure greater than 10 mmHg or 12 mmHg (22, 27–29), lacking the ability to accurately identify more severe cases.

Recently, metabolomics sprung up to be a prospective way of discovering noninvasive biomarkers. Metabolites, as the end products of cellular processes, reflect the change in body condition and hint at the molecular mechanism in the development of diseases. The identification of unique and significantly altered metabolites in patients with SPHT could serve as non-invasive biomarkers for assessing portal pressure. The present study focused on the serum metabolomic alterations in cirrhotic patients with particularly severe PHT (PHT ≥16 mmHg) and identified several new potential biomarkers, providing additional options for the combined application of serum biomarkers in assessing portal pressure. The potential mechanisms driving the progression of PHT through metabolomic analysis were also explored.

Our study is particularly significant as it focuses on the Tibetan population, a group residing in high-altitude areas characterized by chronic hypoxia. This condition not only affects the hematopoietic system but also has implications for other organs. The liver, serving as a central hub for numerous metabolic processes and having a high oxygen demand, is susceptible to structural and functional changes under hypoxic conditions (30). Also, hypoxia-induced inflammation and disruptions in other organs may exert an influence on liver function (30, 31). Previous studies have suggested that hypoxia affects the lipid metabolism of the liver (32). Given these factors, it is plausible that the Tibetan population exhibits unique metabolomic profiles. Nevertheless, there is currently limited research on liver metabolomics among Tibetan populations. Our study addresses this gap by documenting the serum metabolomic profiles of Tibetan patients with liver cirrhosis.

Our study revealed that the majority of the top 30 differential metabolites are lipids and lipid-like molecules, and KEGG pathway analysis also indicated that these differential metabolites are predominantly enriched in pathways related to lipid metabolism. This suggests notable changes in lipid metabolism in SPHT patients compared to MPHT patients. The liver plays a pivotal role in the synthesis, storage, and metabolic processing of lipids and lipoproteins. The previous animal studies indicated that prehepatic PHT impaired liver lipid metabolism, primarily presented as increased lipid deposition and reduced phospholipid synthesis (33, 34). Furthermore, steatosis progressed with the advancement of PHT (33). Neuroendocrine disorder and immunologic factors resulting from cirrhotic PHT may contribute to the altered lipid metabolism. The potential neuroendocrine factors primarily include elevated levels of plasma corticoids, catecholamines, and glucagon. As for the immunologic factors, tumor necrosis factor α (TNF-α) is suggested to exert the most significant impact (33). It can influence lipid metabolism by promoting lipogenesis, inducing lipolysis, inhibiting the activity of lipid metabolism-related enzymes, and regulating cholesterol metabolism and adipokines derived from other adipocytes (35). However, the causal relationship between lipid metabolism disorder and the progression of PHT remains unclear, and they may mutually influence each other causally. Differential metabolites may play a crucial role in this interaction.

S1P is one of the significant differential metabolites. It is a bioactive lipid signaling molecule that participates in regulating inflammation, angiogenesis, vascular permeability, liver regeneration, cancer growth, and metastasis, et al. (19, 36). Inflammation was suspected to be a key mediator of the pathogenesis and severity of PHT (37). Angiogenesis and decreased sinusoidal permeability also play an important role in the pathogenesis of PHT (38). What's more, S1P is a pivotal regulator in sphingolipid metabolism, capable of influencing the progression of liver fibrosis by modulating the hepatic immune response (39). It is reasonable to speculate that PHT-induced alterations in lipid metabolism upregulate S1P, which in turn promotes the progression of PHT. Despite the need for further research to confirm the role of S1P in the progression of PHT, it is still considered a promising biomarker for SPHT, supported by its significant elevation in PHT patients and its high AUC value.

Pisumionoside is a noteworthy differential metabolite categorized under lipids and lipid-like molecules. It is a membrane stabilizer and participates in biological processes including lipid peroxidation, fatty acid metabolism, cell signaling, and lipid metabolism (40). This is consistent with our findings: serum levels of pisumionoside were negatively correlated with blood lipids and glucose levels. These results suggest that elevated pisumionoside is associated with the dysregulated carbohydrate and lipid metabolism resulting from cirrhosis progression. Further research is needed to elucidate how these pathways influence pisumionoside. Although pisumionoside is associated with carbohydrate and lipid metabolism, our study did not observe an enrichment of pisumionoside in these metabolic pathways. Therefore, we tend to consider it as a consequence of PHT progression. Additionally, given its high AUC value, we believe it holds promise as a potential biomarker for SPHT.

N-DG is another differential metabolite with a particularly high AUC, suggesting its potential as a biomarker for SPHT as well. It is an acylglycine with a C-10 fatty acid group as the acyl moiety. It is reported to be elevated in patients with fatty acid oxidation disorders (41). However, our correlation analysis showed that N-DG is not significantly associated with blood lipids. Further research is necessary to explore the reasons behind the elevated N-DG level and its association with lipids metabolism.

KEGG pathway enrichment analysis revealed notable enrichment in the tryptophan metabolism pathway. Both 5-hydroxy-L-tryptophan and serotonin are positioned prominently within this pathway. 5-hydroxy-L-tryptophan, which is both a drug and a natural component of some dietary supplements, can degrade to serotonin (42). Serotonin is involved in various metabolic pathways, such as neuroactive ligand-receptor interaction, bile secretion, cAMP signaling pathway, gap junction, inflammatory mediator regulation of TRP channels, and synaptic vesicle cycle, suggesting a potential close association with the progression of PHT. Studies have reported that serotonin can modulate portal and sinusoidal blood flows (43). Injecting serotonin into the portal vein markedly increases portal vein pressure (44). Given the significant role of serotonin in the progression of PHT, elucidating the mechanisms underlying elevated serotonin levels in cirrhosis may aid in controlling the advancement of PHT. On one hand, elevated serotonin may be associated with hepatocyte damage during liver cirrhosis. Our correlation analysis showed that serotonin levels are positively correlated with serum ALT levels, which are released from damaged hepatocytes. Studies indicate that serotonin plays a crucial role in liver regeneration. Serotonin derived from PLT promotes liver regeneration following partial hepatectomy (45). Therefore, increased serotonin levels may be a result of the repair response to hepatocyte damage. However, elevated serotonin levels may promote the development of liver cirrhosis through various mechanisms we previously mentioned. On the other hand, in the periphery, most of the serotonin is synthesized by enterochromaffin

cells located in the gut (46). It is widely acknowledged that microbial products play a significant role in influencing gut function (47). The synthesis and release of serotonin by enterochromaffin cells in the gut are influenced by intestinal microbiota through the production of short-chain fatty acids. Simply put, acetate and butyrate, produced by gut microbes from the fermentation of dietary sugars, boost the expression of TpH1 mRNA and raise serotonin production by enterochromaffin cells (48). The gut microbiota of patients with cirrhosis undergoes alterations, with distinct differences between compensated and decompensated stages (49). The gut microbiota of patients with portal hypertension was also different from other populations (50). However, the exact link between PHT and gut microbiota remains elusive. Additionally, differences in gut microbiota among patients with PHT at different stages have not been reported. Our study suggests that serotonin may serve as a key molecule bridging the gap between gut microbiota and the progression of PHT. Further research is required to elucidate which microbiota and their metabolites play pivotal roles in the progression of PHT.

Linoleic acid metabolism was remarkably disturbed in SPHT. The significantly elevated linoleic acid metabolites (13(S)-HpODE, 13-OxoODE, and linoleic acid) in SPHT patients in the present study hint at their role in the progression of PHT. Changes in linoleic acid metabolism have been reported in cirrhosis patients previously. Some studies found a decreased linoleic acid level in cirrhotic patients (51, 52). While EKODE, the metabolites from linoleic acid metabolism, was reported to be increased in patients with acutely decompensated cirrhosis and acute-on-chronic liver failure and be associated with a 28-day mortality of cirrhosis (53). In total, linoleic acid metabolism is suggested to play a critical role in influencing the incidence and progression of liver cirrhosis.

Our research also confirms that the TCA cycle is significantly disordered in patients with SPHT. Perturbations of TCA cycle metabolism have been reported to occur from the onset of liver fibrosis in carbon tetrachloride-induced fibrosis animal models (54). The TCA cycle is the ultimate common oxidative pathway for lipids, carbohydrates, and amino acids and it is the most important pathway connecting almost all metabolic pathways (55). Existing research has shown that the TCA cycle promotes insulin resistance and fatty liver by inducing mitochondrial dysfunction (56). This is consistent with the result of our correlation analysis, where metabolites of the TCA cycle were positively correlated with blood lipid levels. The inflammatory environment in cirrhotic PHT may lead to remodeling of the TCA cycle, resulting in alterations in the pro-inflammatory and anti-inflammatory metabolites (57). Our study uncovered a notable increase in citrate, one of the metabolites of the TCA cycle, in the peripheral serum of cirrhotic patients with SPHT. Citrate plays a crucial role in bridging carbohydrate and fatty acid metabolism, as well as in protein modification. Moreover, citrate functions as a significant inflammatory signal, modulating dendritic cell activation and the production of pro-inflammatory factors (58). Previous studies have shown a positive correlation between circulating citrate levels and the degree of liver fibrosis, with citrate levels increasing as fibrosis worsens (59). However, there is a lack of relevant research on citrate in PHT. Our study suggests that citrate may play a crucial role in the progression of PHT. Nevertheless, the elevation of citrate is a protective feedback response to inflammation and injury or a factor promoting PHT requires further investigation.

Although our study has identified potential biomarkers for SPHT and molecules that may be associated with the progression of PHT, there are some limitations to our research. A primary limitation is the small sample size. Expanding the sample size would be critical for further verifying the roles of these metabolites. Also, the diagnostic specificity and sensitivity of these biomarkers, in comparison to existing ones, need further investigation. Additionally, the roles of the metabolites in the progression of PHT require further investigation to be clearly defined.

Conclusion

Tibetan cirrhotic patients who suffer from SPHT exhibit a distinct metabolomic profile compared to those with MPHT. Key metabolites such as pisumionoside and N-DG demonstrate high AUC values, showcasing their significant potential as biomarkers for SPHT. Additional metabolites including 6-(4-ethyl-2-methoxyphenoxy)-3,4,5-trihydroxyoxane-2-carboxylic acid, S1P, 4-hydroxytriazolam, 4,5-Dihydroorotic acid, 6-Hydroxy-1H-indole-3-acetamide, 7alpha-(Thiomethyl)spironolactone, 6-Deoxohomodolichosterone, Glutaminylisoleucine, Taurocholic acid 3-sulfate, and Phe Ser also emerge as promising biomarkers for SPHT. Notably, certain lipid metabolites, particularly S1P, are significantly elevated in SPHT patients, indicating that disruptions in lipid metabolism may be a key factor in the progression of PHT. Furthermore, metabolic pathways such as tryptophan metabolism, linoleic acid metabolism, and the citrate cycle are intricately linked with the pathophysiology of liver cirrhosis and PHT. These pathways may play pivotal roles in the progression of PHT. Further studies are essential to corroborate the influence of these metabolic pathways on PHT development and to decipher their specific molecular mechanisms.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

The studies involving humans were approved by Ethics Committee of Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region (Research No. 64 of the Year 2020). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YY: Conceptualization, Visualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft. CX: Visualization, Investigation, Funding acquisition, Writing – original draft, Methodology, Formal analysis. HoH: Writing

– original draft, Visualization, Software, Methodology. ST: Writing – original draft, Visualization, Software, Methodology, Funding acquisition. HuH: Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

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Conflict of 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1404442/full#supplementary-material

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Prognostic nomogram based on the gamma-glutamyl transpeptidase-to-platelet ratio for patients with compensated cirrhotic hepatocellular carcinoma after local ablation

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Background: Hepatocellular carcinoma (HCC) patients with compensated cirrhosis typically face a high prevalence and unfavorable prognosis. However, there is currently a deficiency in prediction models to anticipate the prognosis of these patients. Therefore, our study included the Gamma-glutamyl transpeptidase-to-platelet ratio (GPR) in analysis and aimed to develop a nomogram for HCC patients with compensated cirrhosis after local ablation.

Methods: Enrolling 669 patients who underwent local ablation at Beijing You'an Hospital during the period from January 1, 2014, to December 31, 2022, this study focused on individuals with compensated cirrhotic HCC. In a ratio of 7:3, patients were allocated to the training cohort (n=468) and the validation cohort (n=201). Lasso-Cox regression was employed to identify independent prognostic factors for overall survival (OS). Subsequently, a nomogram was constructed using these factors and was validated through receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA).

Results: GPR, age, and hemoglobin were identified by Lasso-Cox regression as independent prognostic factors of the nomogram. The area under the ROC curves (AUCs) for 3-, 5-, and 8-year OS (0.701, 0.755, and 0.768 for the training cohort; 0.684, 0.707, and 0.778 for the validation cohort), and C-indices (0.695 for training cohort; 0.679 for validation cohort) exhibited the excellent predictive ability of the nomogram. Calibration curves and DCA curves indicated favorable calibration performance and clinical utility. Patients were further stratified into two risk groups according to the median nomogram score. There existed an obvious distinction between the two groups both in the training cohort and validation cohort.

Conclusion: In summary, this research established and validated a novel nomogram to predict OS, which had good predictive power for HCC patients with compensated cirrhosis after local ablation.

KEYWORDS

hepatocellular carcinoma (HCC), compensated cirrhosis, overall survival (OS), nomogram, gamma-glutamyl transpeptidase-to-platelet ratio (GPR)

Introduction

Hepatocellular carcinoma (HCC), accounting for more than 90% of primary liver cancer cases, poses a significant threat to human health (1, 2). Based on statistical data, HCC ranks as the sixth most common cancer and the third leading cause of cancer-related death globally (3). Liver cirrhosis stands as a major risk factor for the development of HCC, with 80-90% of detected HCC cases occurring in cirrhotic patients (4, 5). There are approximately 112 million cases of compensated cirrhosis worldwide based on the latest Global Burden of Disease report in 2017, with an annual HCC incidence of 2.2-5% (6, 7). Considering the high prevalence and poor prognosis of compensated cirrhosis in HCC patients, prognostic models to predict overall survival are crucial for these individuals.

Local ablation is considered as a first-line treatment for patients with early-stage HCC, and patients' survival has improved due to the advances of this therapeutic modality these years (8). As a minimally invasive approach, it has advantages such as small incisions, and less trauma, bleeding, and complications (9). However, the prognosis of HCC is still unsatisfactory after ablation, with a 5-year overall survival of 30-40% (10, 11). Therefore, our study focused on the patients who received local ablation.

It has been widely acknowledged that the inflammatory response, which reflects cancer status and affects the progression of tumors, is apparently interconnected with the tumor microenvironment (12). Gamma-glutamyl transpeptidase (GGT)-to-platelet (PLT) ratio (GPR), an inflammatory marker, was proposed in the past few years as an innovative predictor for liver disease (13). Numerous studies have substantiated the predictive capability of GPR in predicting cirrhosis in patients with hepatitis B virus (HBV) infection and recognized it as an independent prognostic factor for HCC (14, 15). A study by Yang et al. observed that the specific value of GPR was selected as 0.30, which had favorable efficiency for distinguishing high-risk patients (16). Nevertheless, as for HCC patients with compensated cirrhosis, the predictive capability of GPR for prognosis remains uncertain. Additionally, there is also lacking effective nomograms to predict patients' mortality rates.

Therefore, this study included GPR in the analysis and investigated its association with overall survival. Subsequently, a nomogram for HCC patients with compensated cirrhosis after local ablation was built based on demographic and clinical variables selected by Lasso-Cox regression. Moreover, the comparison of survival times among different risk groups derived from the established nomogram was done, aiming to facilitate the identification of high-risk populations and offer more precise clinical guidance.

Methods

Patients

We retrospectively analyzed the clinical data of HCC patients with compensated cirrhosis who received ablation therapy at Beijing You'an Hospital affiliated with Capital Medical University between January 1, 2014, and December 31, 2022. A total of 669 patients were included in the final analysis and these patients were randomly assigned to two groups in a ratio of 7:3, with 468 patients in the training set and 201 in the validation set (Supplementary Figure S1). This study obtained approval from the Ethics Committee of Beijing You'an Hospital affiliated with Capital Medical University, and informed consent was waived due to the retrospective nature of the study.

Patients were diagnosed with HCC and cirrhosis according to the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) (17, 18). The early-stage of HCC was defined according to Barcelona Clinic Liver Cancer (BCLC) stage and Child-Pugh stage (19, 20). Compensated cirrhosis was defined as cirrhosis in the absence of clinical complications, including ascites, variceal bleeding, and hepatic encephalopathy.

The inclusion criteria were as follows: (1) age from 18 to 75 years; (2) BCLC stage 0 or A; (3) Child-Pugh stage A; (4) HCC patients with compensated cirrhosis. The exclusion criteria were as follows: (1) incomplete clinical or follow-up data; (2) with distant metastases or other malignancies; (3) insufficiency of vital organs; (4) bacterial or viral infections; (5) rheumatism or blood disorders that can cause platelet changes.

Data collection and follow-up

Demographics and laboratory data were collected from the electronic patient records, including age, gender, medical history (smoking, drinking, antiviral treatment, hypertension, diabetes mellitus), BCLC stage, tumor number, tumor size, red blood cell (RBC), hemoglobin (Hb), white blood cell (WBC), alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total bilirubin (TBIL), direct bilirubin (DBIL), neutrophils (Neu), lymphocytes (Lym), monocytes (Mon), albumin (Alb), globulin (Glob), prealbumin (Palb), prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (APTT), and international normalized ratio (INR). Meanwhile, we included the gamma-glutamyl transpeptidase to platelet ratio (GPR) in our analysis to increase the prognostic value of the proposed nomogram.

A close follow-up of all patients after local ablation was conducted, and it was completed via outpatient consultation or telephone calls. The typical follow-up was performed every 3 months in the first year and then every 6 months thereafter, which comprised physical examination, laboratory tests, and imaging examination. The last day of follow-up was July 1, 2023. Overall survival (OS), as the primary endpoint of this study, was defined as the interval from local ablation to either the occurrence of death or the last follow-up.

Ablation procedure

All enrolled patients were treated with local ablation, which was performed by qualified hepatologists and interventional radiologists. The specific process includes 5 items: (1) Appropriate position for ablation was determined by computed tomography (CT) or magnetic resonance imaging (MRI). (2) The ablation needle was inserted in the marked skin, and followed by image scanning to track the ablation process. (3) For the purpose of attaining complete ablation, operators should expand the ablative range and contemplate multiple sites, overlapping, or repeated ablation. (4) In order to prevent tumor implantation and postoperative bleeding, the needle track required to be heated in the final stage. (5) Following the ablation, all patients underwent imaging examinations to assess treatment efficacy and possible complications.

The methods of local ablation include radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation, among others. By introducing radiofrequency electrodes directly into the tumor tissue, RFA utilizes high-frequency electrical currents to generate heat, resulting in necrosis. While MWA uses microwave energy to generate heat and kill tumor cells. The characteristic of microwave energy is their ability to rapidly and evenly heat tissues. As for cryoablation, it utilizes extremely low temperature of medium (such as liquid nitrogen or argon gas) to freeze and destroy tumor cells. These ablation therapeutic modalities have specific advantages in the treatment of cancer, and the specific method was selected by clinical physicians in our study.

Statistical analysis

Continuous variables were presented as mean and standard deviation (mean ± SD) and analyzed by Student's t-test or non-parametric test. Categorical variables were expressed as frequency (percentage) and contrasted using the Chi-square test.

In this research, patients were randomly split into the training set (n=468) and validation set (n=201) in a ratio of 7:3. The training cohort was utilized for building the nomogram, while the validation cohort was specifically employed to verify its performance. Concurrently, Lasso regression and multivariate Cox regression analysis were used to determine the independent risk factors associated with OS. Significant factors with p-values below the threshold of 0.05 were included in the nomogram. Subsequently, patients were categorized into low-risk group and high-risk group according to the scores calculated from the nomogram. Kaplan-Meier curves and log-rank tests were then employed to compare OS between the two groups. Additionally, the receiver operating characteristic (ROC) curves were plotted and the area under the ROC curves (AUCs) was calculated to evaluate the discriminative ability. Model calibration and clinical utility were assessed by calibration curves and decision curve analysis (DCA), respectively. At last, we used the ROC curve to observe the predictive ability of GPR and other risk factors.

All analyses were conducted using R statistical software (version 4.1.2) in this study. Statistical significance was set at $p<0.05$ (two-tailed).

Results

Baseline characteristics

During the period from January 1, 2014, to December 31, 2022, a total of 669 HCC patients with compensated cirrhosis after local ablation were recruited in this study and randomized into two groups with a 7:3 ratio. There were 468 patients constituted the training set, while 201 formed the validation set. All patients received ablation therapy without any combined treatments, and there were 150 (22.4%) patients died during the follow-up period. Our study concluded patients' last follow-up on July 1, 2023, with a median follow-up duration of 52.4 months.

The baseline clinical characteristics of all patients were presented in Table 1, which revealed no statistical differences between the two groups ($p>0.05$). Among these patients, the average age was 56.28 years, with 544 (81.3%) males and 125 (18.7%) females. Notably, 285 (42.6%) patients had a history of smoking and 215 (32.1%) had a history of drinking. Furthermore, 185 (27.7%) individuals were diagnosed with hypertension and 133 (19.9%) with diabetes mellitus. The training and validation cohorts both had a majority of patients in BCLC stage A (71.2% vs. 65.2%), with most solitary tumors (68.4% vs. 71.1%) and tumor size less than 3cm (65.6% vs. 60.1%).

TABLE 1 Clinical characteristics for training and validation cohorts.

Characteristic	Training cohort (N=468)	Validation cohort (N=201)	P value
Age	56.25 ± 9.32	56.35 ± 9.37	0.896
Gender (%)			0.904
Male	380 (81.2)	164 (81.6)	
Female	88 (18.8)	37 (18.4)	
Hypertension (%)			0.649
Yes	127 (27.1)	58 (28.9)	
No	341 (72.9)	143 (71.1)	
Diabetes (%)			0.403
Yes	97 (20.7)	36 (17.9)	
No	371 (79.3)	165 (82.1)	
Antiviral (%)			0.159
Yes	288 (61.5)	112 (55.7)	
No	180 (38.5)	89 (44.3)	
Smoking (%)			0.456
Yes	195 (41.7)	90 (44.8)	
No	273 (58.3)	111 (55.2)	
Drinking (%)			0.060
Yes	140 (29.9)	75 (37.3)	
No	328 (70.1)	126 (62.7)	
BCLC (%)			0.124
0	135 (28.8)	70 (34.8)	
A	333 (71.2)	131 (65.2)	
T.N. (%)			0.477
Single	320 (68.4)	143 (71.1)	
Multiple	148 (31.6)	58 (28.9)	
T.S. (%)			0.251
<3cm	307 (65.6)	141 (70.1)	
≥3cm	161 (34.4)	60 (29.9)	
GPR	0.67 ± 0.72	0.61 ± 0.56	0.284
RBC (10^12/L)	4.31 ± 0.58	4.28 ± 0.47	0.443
Hb (g/L)	134.63 ± 18.95	133.79 ± 16.42	0.584
WBC (10^9/L)	5.29 ± 2.12	5.16 ± 1.90	0.477
Neu (10^9/L)	3.40 ± 1.84	3.23 ± 1.60	0.230
Lym (10^9/L)	1.33 ± 0.64	1.38 ± 0.67	0.354
Mon (10^9/L)	0.42 ± 0.24	0.42 ± 0.22	0.948
ALT (U/L)	31.34 ± 18.33	32.44 ± 18.77	0.478
AST (U/L)	30.48 ± 12.69	31.91 ± 16.27	0.222
ALP (U/L)	84.92 ± 32.39	84.36 ± 29.51	0.834
TBIL (umol/L)	17.16 ± 7.73	16.84 ± 7.39	0.626
DBIL (umol/L)	5.58 ± 3.19	5.44 ± 3.48	0.611
Alb (g/L)	38.20 ± 3.98	38.35 ± 3.80	0.643
Palb (U/L)	150.36 ± 55.56	145.36 ± 52.95	0.280
Glob (g/L)	28.11 ± 4.71	28.09 ± 5.44	0.962
APTT (s)	33.09 ± 4.03	33.09 ± 3.87	0.995
PT (s)	12.35 ± 1.19	12.29 ± 1.28	0.587
TT (s)	15.56 ± 2.10	15.70 ± 2.17	0.465
INR	1.10 ± 0.10	1.09 ± 0.11	0.390

Continuous variables were presented as mean and standard deviation (mean ± SD). Categorical variables were expressed as frequency (percentage).
BCLC, Barcelona Clinic Liver Cancer; T.N., tumor number; T.S., tumor size; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; RBC, red blood cell; Hb, hemoglobin; WBC, white blood cell; Neu, neutrophil; Lym, lymphocyte; Mon, monocyte; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin; Alb, albumin; Palb, prealbumin; Glob, globulin; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; INR, international normalized ratio.

Independent prognostic factors for OS

Lasso regression, utilizing a loss function with L1 regularization to penalize model coefficients while minimizing the objective function, was employed to screen risk factors associated with OS (Figure 1). The 10-fold cross-validation method was applied to select the optimal λ value, which was determined to be 0.0274 (Log λ = -1.562). Significant risk factors filtered by Lasso regression were GPR, age, gender, history of antiviral therapy, history of drinking, tumor number, tumor size, BCLC stage, Hb, and Palb. These variables were further incorporated into the multivariable Cox regression analysis, revealing that GPR (HR:1.257, 95% CI: 1.037-1.527), age (HR:1.025, 95% CI: 1.003-1.048), and Hb (HR:0.988, 95% CI: 0.978-0.999) as the independent prognostic factors for OS (Table 2).

Development of the nomogram

Based on these independent prognostic factors, we constructed a nomogram for predicting the OS of compensated cirrhotic HCC patients who received local ablation (Figure 2). Every risk factor corresponds to a specific score according to its value on the nomogram. It was necessary to sum the scores of factors and draw a vertical line at the corresponding total point. After these steps, the vertical line intersects with three lines representing mortality risk, which forecast the 3-, 5-, and 8-year OS.

In the training cohort, patients were categorized into low-risk group (n=234) and high-risk group (n=234) in light of the nomogram. The Kaplan-Meier curve was plotted, indicating that the median OS was 92.0 months for the high-risk group, while it was not reached in the low-risk group (Figure 3). The cumulative OS rates for 3-, 5-, and 8-year were 86.9%, 71.0%, and 49.5% in the

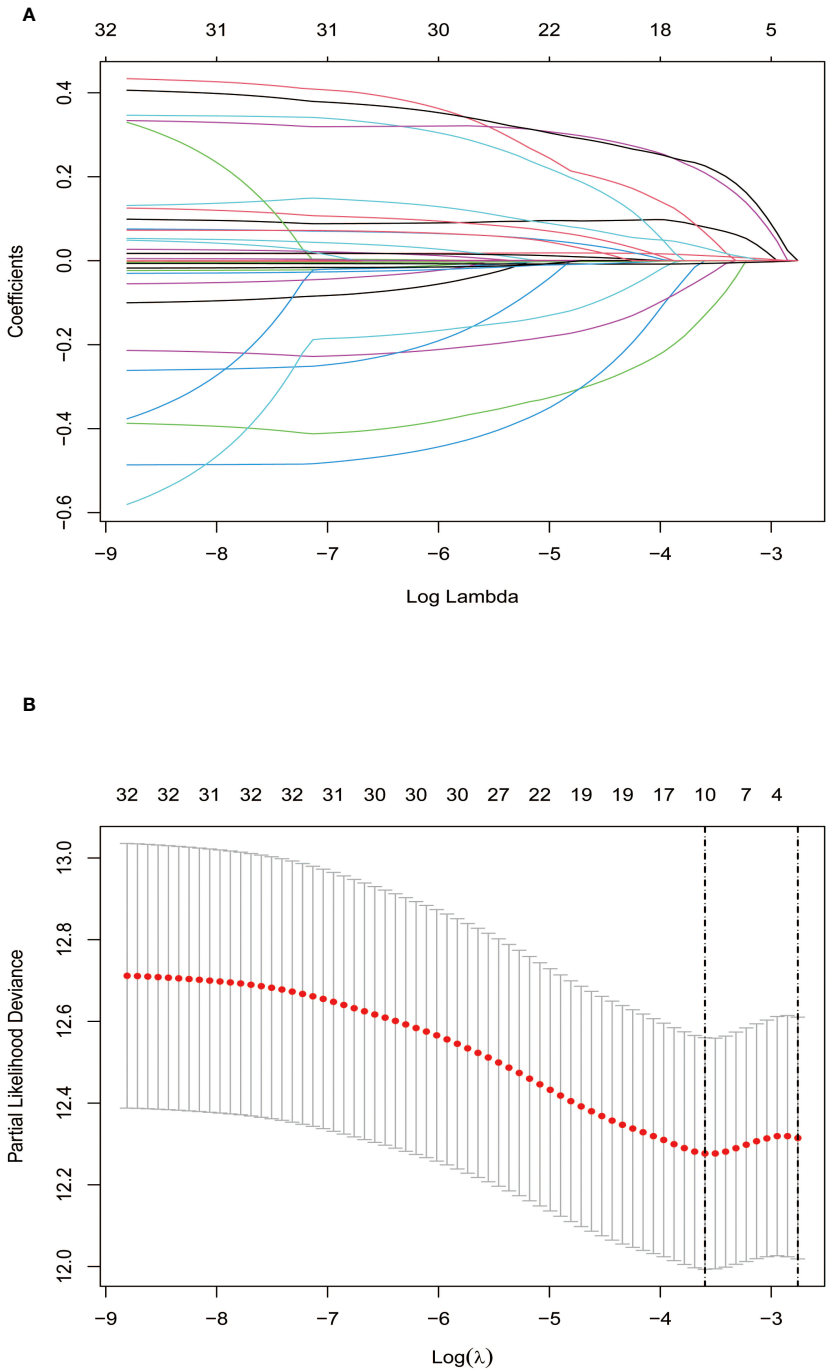

FIGURE 1
Screening of independent prognostic factors based on Lasso regression. **(A)** The variation characteristics of the coefficient of variables; **(B)** The selection process of the optimum value of the parameter λ by cross-validation method.

high-risk group, while 94.0%, 87.3%, and 70.6% in the low-risk group. There existed an obvious distinction in OS among the two groups (p=0.00034).

Subsequently, the time-dependent ROC curve was drawn and the C-index in the training set was 0.695 (95% CI: 0.656-0.734). It showed that AUCs of 3-, 5-, and 8-year were 0.701, 0.755, and 0.768. The 1-specificity and sensitivity of 3-, 5-, and 8-year were (0.468, 0.862), (0.411, 0.913), and (0.331, 0.861), respectively (Figure 4). These outcomes highlighted the advantageous discriminative ability. At last, a calibration curve (Figure 5) and DCA curves (Figure 6) were created, affirming that the nomogram demonstrated good calibration and clinical utility.

Validation of the nomogram

In order to further validate the reliability of this nomogram, we performed internal validation in our study. According to the

TABLE 2 Multivariate Cox regression analysis based on the results of Lasso regression.

Variables	HR (95%CI)	P value
GPR	1.257 (1.037-1.527)	**0.020**
Age	1.025 (1.003-1.048)	**0.024**
Gender	0.654 (0.361-1.186)	0.162
Antiviral	0.826 (0.558-1.222)	0.338
Drinking	1.340 (0.881-2.037)	0.172
BCLC	1.139 (0.608-2.134)	0.845
T.N.	1.421 (0.912-2.214)	0.121
T.S.	1.398 (0.891-2.193)	0.146
Hb	0.988 (0.978-0.999)	**0.031**
Palb	0.998 (0.994-1.002)	0.356

Bolded values indicate a P-value less than 0.05, which represent statistical significance.
HR, hazard ratio; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; BCLC, Barcelona Clinic Liver Cancer; T.N., tumor number; T.S., tumor size; Hb, hemoglobin; Palb, prealbumin.

nomogram, patients in the validation cohort were also classified into two groups by the Kaplan-Meier curve: low-risk group (n=100) and high-risk group (n=101) (Figure 3). The median OS was 92.0 months for the high-risk group, while it was not reached in the low-risk group. The cumulative OS rates for 3-, 5-, and 8-year were 85.2%, 71.3%, and 49.8% in the high-risk group, while 95.2%, 86.5%, and 82.6% in the low-risk group. In concordance with the training cohort, there was also a statistically significant discrepancy in OS among the two groups (P=0.0021).

The C-index in the validation cohort was 0.679 (95% CI: 0.616-0.742) and the AUCs for 3-, 5-, and 8-year were 0.684, 0.707, and 0.778, which suggested the favorable diagnostic value. The 1-specificity and sensitivity of the ROC curve were (0.472, 0.832), (0.434, 0.844), and (0.351, 0.903) for 3-, 5-, and 8-year (Figure 4). The calibration curve exhibited a good match (Figure 5), and the DCA curves also had good clinical practicability (Figure 6).

The predictive performance of the GPR

The discriminative ability of the GPR and other risk factors was assessed using ROC curve (Supplementary Figure S2). The AUC values were 0.514 for age, 0.504 for hemoglobin, 0.580 for fibrosis 4 score (Fib-4), 0.614 for aspartate transaminase to platelet ratio index (APRI), and 0.652 for GPR, respectively. The outcome indicated that the GPR was observed to have better predictive ability compared with other risk factors. Moreover, we explored the AUC value of the combination of GPR and neutrophil to lymphocyte ratio index (NLR) based score (AUC=0.679), which showed improved discriminability compared to GPR alone. Thus, the predictive ability of GPR combined with NLR need more studies to investigate.

The predictive performance of the nomogram for DFS

At last, our study used KM curves to analyze the predictive ability of the nomogram for disease-free survival (DFS). It was defined as the time from the date of local ablation to recurrence or last of follow-up. Although it underperformed in the validation

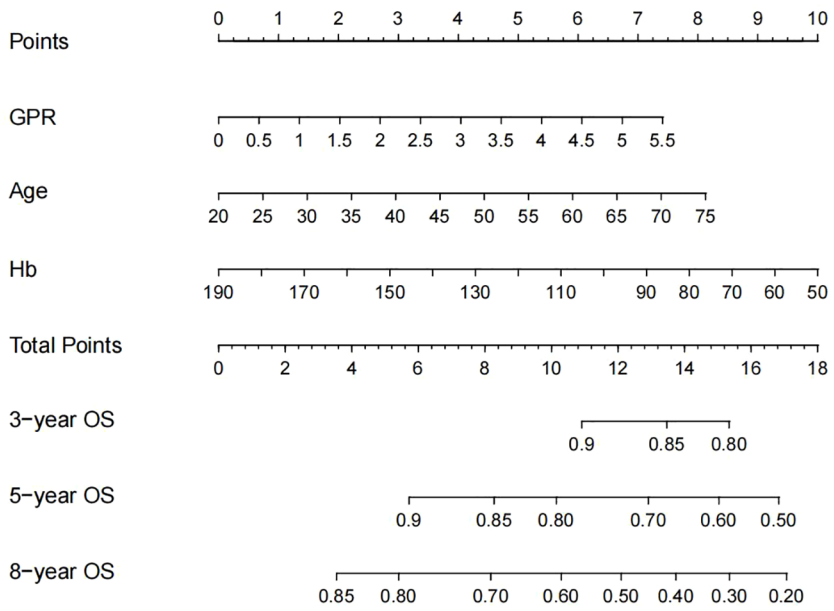

FIGURE 2
Nomogram, including GPR, age, and Hb for 3-, 5-, and 8-year OS in HCC patients with compensated cirrhosis. GPR, gamma-glutamyl transpeptidase-to-platelet ratio; Hb, hemoglobin; OS, overall survival; HCC, hepatocellular carcinoma.

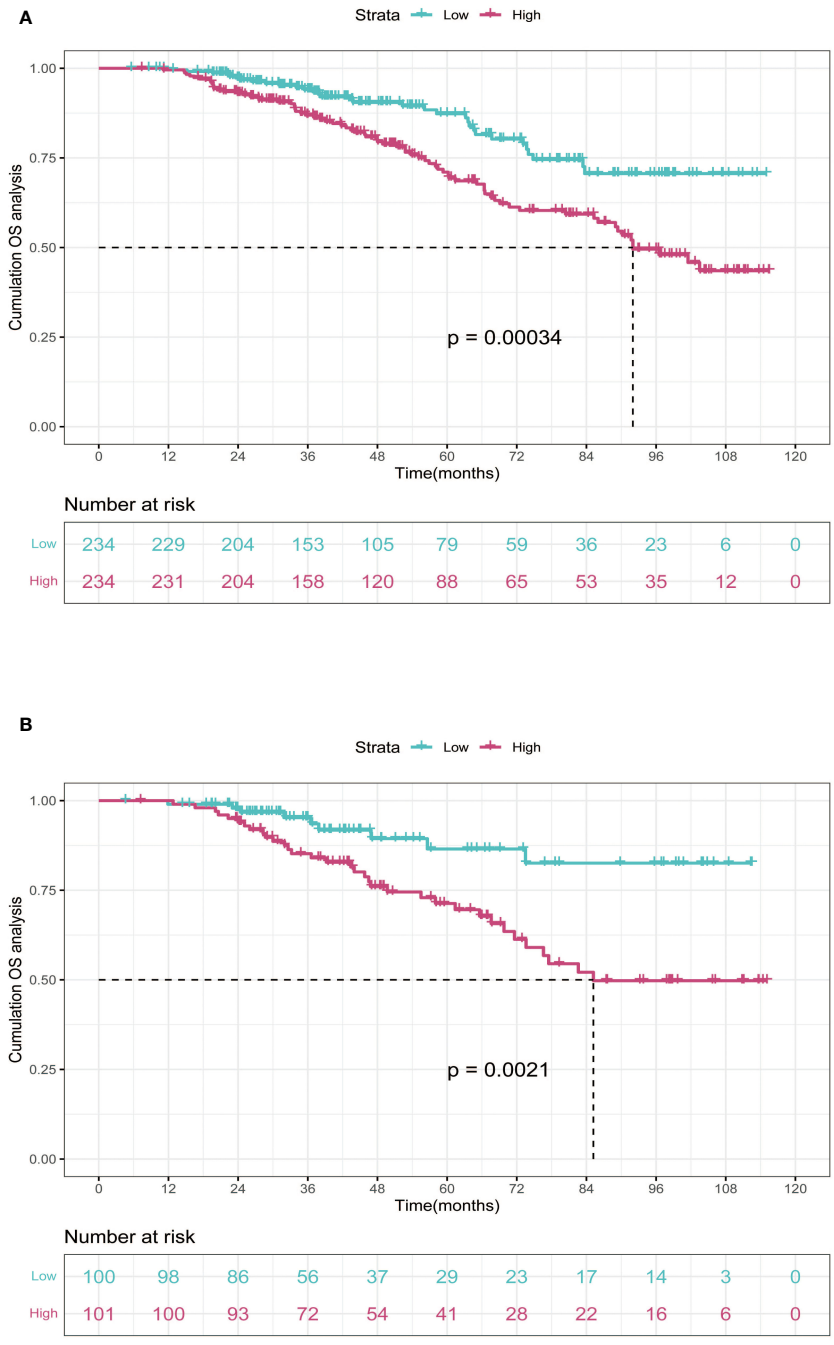

FIGURE 3
Kaplan-Meier curves of OS for two risk groups classified by the median nomogram score in training and validation cohort. **(A)** training cohort; **(B)** validation cohort. OS, overall survival.

cohort, there existed an obvious distinction among training cohort (Supplementary Figure S3). In the training cohort, the median DFS was 18.0 months for the high-risk group, and 24.5 months for the low-risk group. The cumulative DFS rates for 1-, 3-, and 5-year were 66.2%, 24.6%, and 16.8% in the high-risk group, while 73.9%, 35.4%, and 26.0% in the low-risk group. These outcomes demonstrated that the nomogram had a certain predictive capability for DFS.

Discussion

Despite significant progress regarding the treatment of HCC in recent years, the prognosis for this malignancy continues to be unfavorable (21). Liver cirrhosis, especially compensated liver cirrhosis, has a substantial number of patients worldwide (6). It remains a main etiological factor for the development of HCC, which seriously impacts the life quality of patients (22). Thus, our

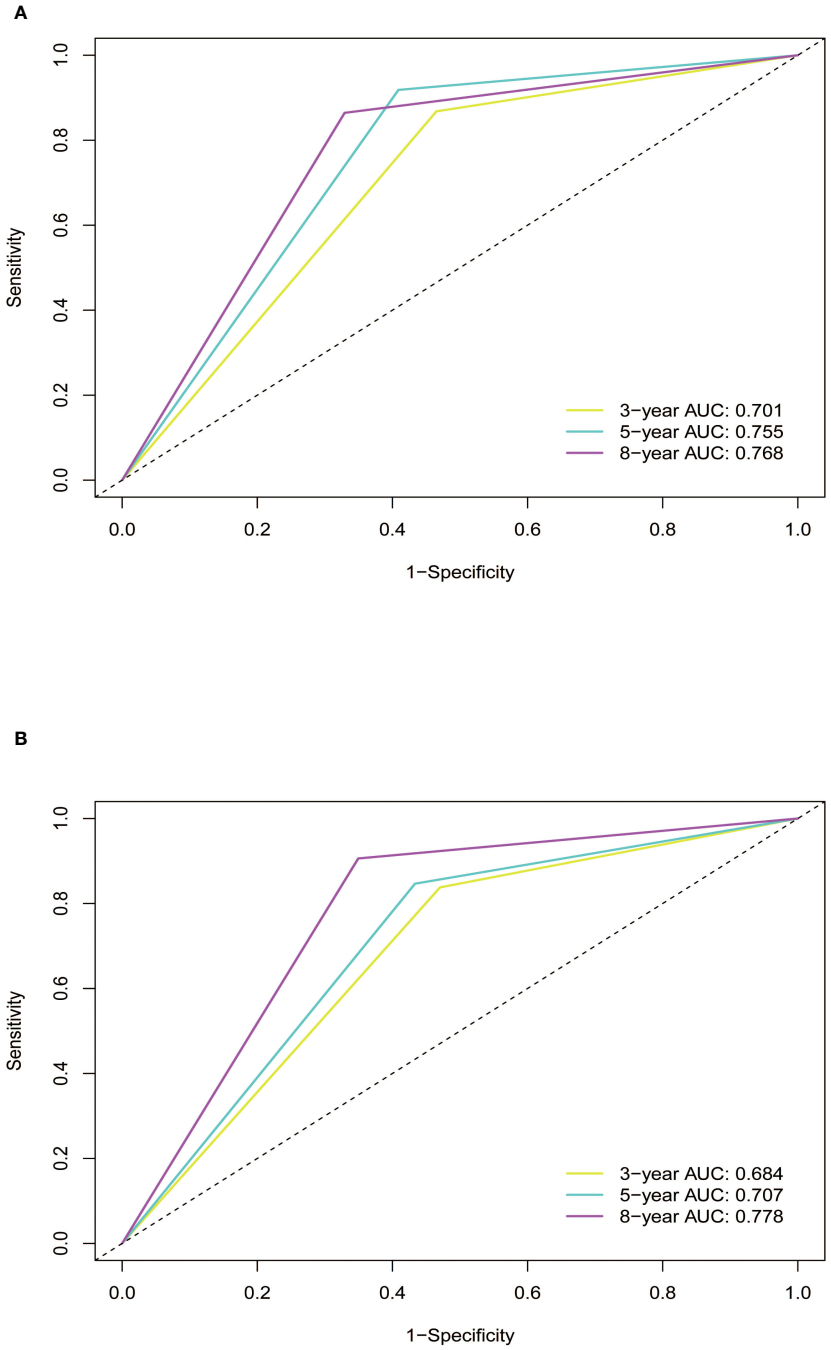

FIGURE 4
ROC curves of the nomogram in training and validation cohort. **(A)** In the training cohort, the AUCs for 3-, 5- and 8-year OS were 0.701, 0.755, and 0.768, respectively. **(B)** In the validation cohort, the AUCs for 3-, 5- and 8-year OS were 0.684, 0.707, and 0.778, respectively. ROC, receiver operating characteristic curve; AUC, area under the ROC curve; OS, overall survival.

study concentrated on compensated cirrhotic patients with HCC and developed a nomogram for OS to help guide clinical decision-making. The current nomogram exhibited effective predictive performance, as indicated by AUCs, C-indexes, calibration curves, and DCA plots.

The treatment modalities for HCC are diverse and typically based on the patients' health status and the stage of the tumor. Conventional methods include surgical resection, local ablation, anti-angiogenesis therapy, immunotherapy, and second-line treatments (23). Local ablation, encompassing techniques such as RFA, MWA, and cryoablation, holds a prominent position in the treatment of HCC. The ablation process involves inserting an ablation needle into tumor tissues under the guidance of imaging techniques, and high-frequency radio waves are applied to damage HCC cells (24). Several studies have demonstrated that local ablation provides effective therapy for patients with early-stage HCC during long-term clinical practice experience (25, 26). Nevertheless, the prognosis after ablation remains unfavorable, and deserves further investigation.

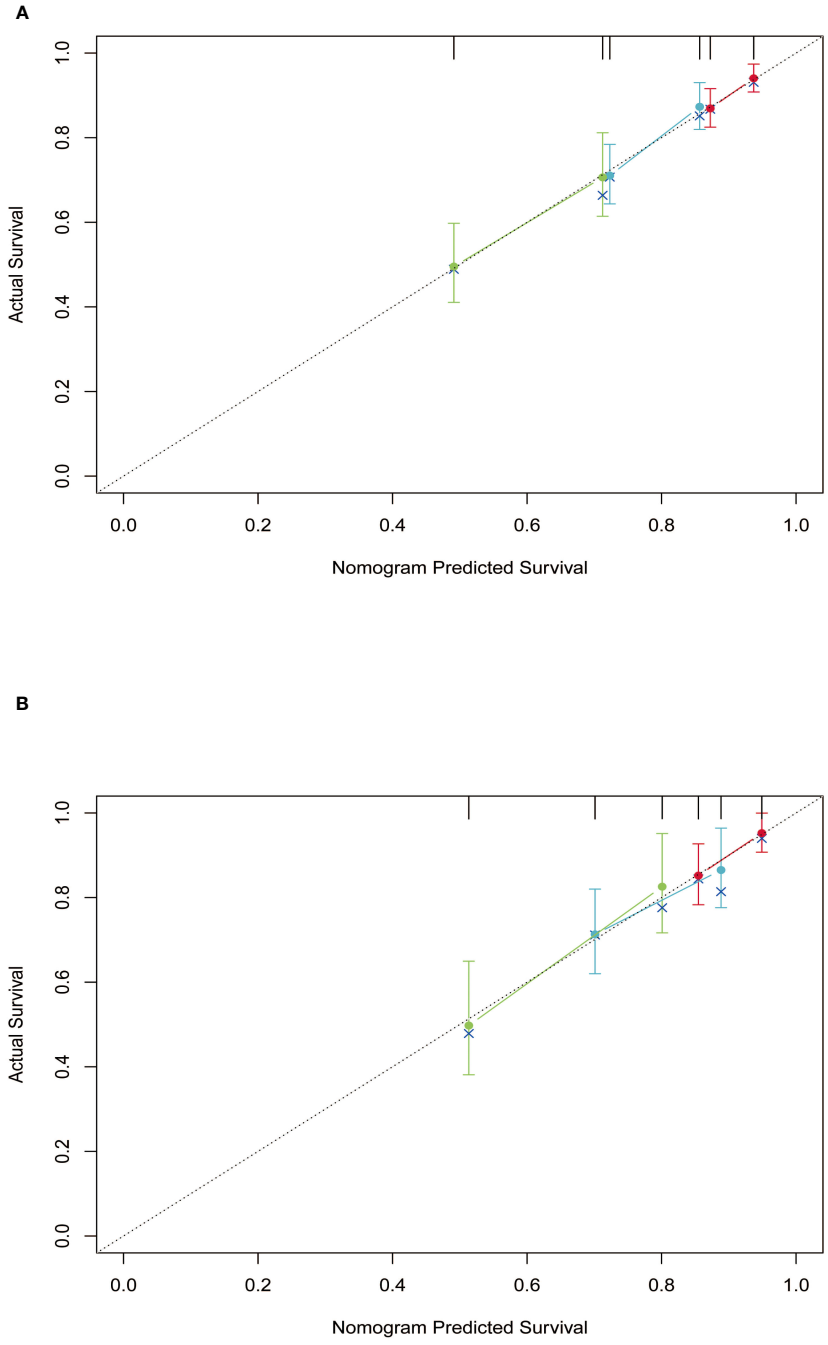

FIGURE 5
Calibration curves of the nomogram in training and validation cohort. **(A)** training cohort; **(B)** validation cohort.

In this study, we employed Lasso regression to identify independent prognostic factors and construct a nomogram. This approach regulates the rigor of feature selection by adjusting the regularization parameter λ, facilitating the screening of features, and reducing the dimensionality of the prediction model. It enables more effective exploration of voluminous and complex datasets and somewhat addresses the limitations in overfitting and multicollinearity (27, 28). The nomogram developed by Lasso regression can assist in identifying patients with a high risk of mortality, and effectively improve the prognosis through early intervention. Meanwhile, developing personalized treatment plans based on the different prognoses of HCC patients could efficiently allocate medical resources and achieve precision medicine.

A crucial prognostic factor in the nomogram is GPR, which objectively indicates the combination of coagulation status and liver function. Initially introduced in 2015 by Lemoine et al. for the clinical evaluation of HBV-related hepatic cirrhosis, GPR serves as a more precise routine laboratory marker than the aspartate transaminase-to-platelet ratio index (APRI) and Fib-4 for staging liver fibrosis in patients with chronic HBV infection (13). A retrospective study,

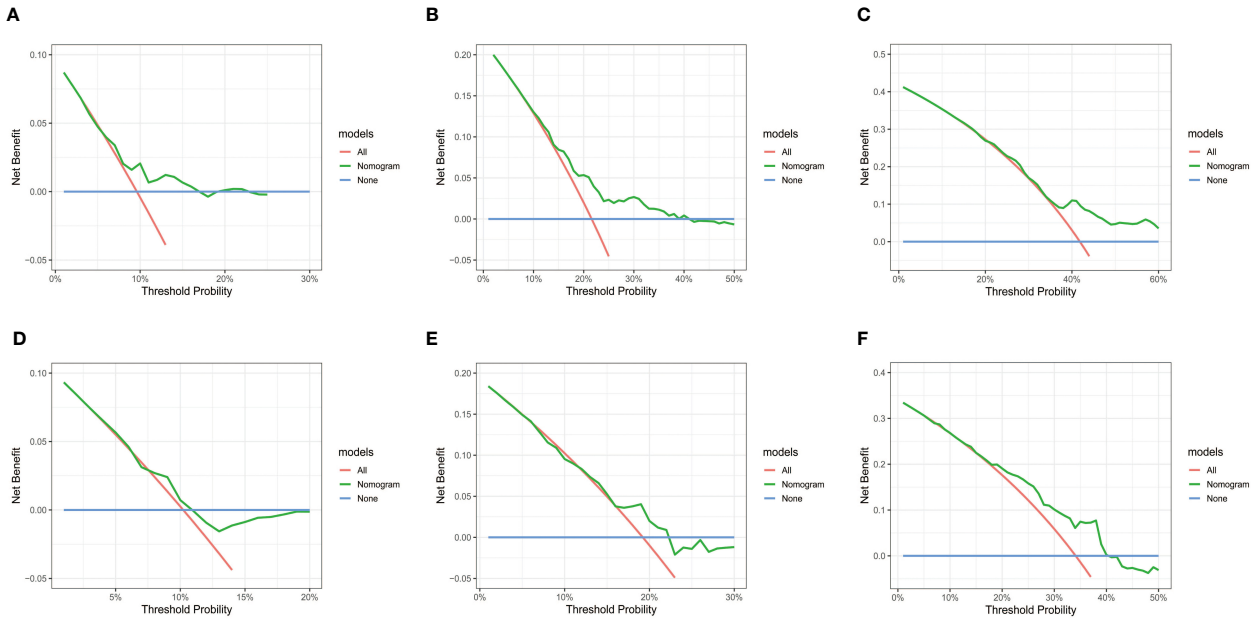

FIGURE 6
DCA curves of the nomogram in training and validation cohort. **(A-C)** DCA for 3-, 5- and 8-year OS in training cohort. **(D-F)** DCA for 3-, 5- and 8-year OS in validation cohort. DCA, decision curve analysis; OS, overall survival.

involving 182 patients with HBV-associated HCC, investigated the prognostic significance of GPR. The findings revealed that a high level of GPR was associated with unfavorable recurrence-free survival and overall survival (29). Similarly, research by Wang et al. also acknowledged the value of GPR in the prognosis of HCC patients and established a predictive model. As an inflammation-related factor, GPR independently correlated with the survival of HCC patients who underwent hepatectomy (30).

Notably, GGT is a notable enzyme located in cell membranes and actively participates in glutathione metabolism (31). Functioning as a crucial antioxidant, it plays a pivotal role in the protection of liver cells from the detrimental effects of oxidative stress (32). An elevated GGT level not only signals liver damage but also contributes to the development of HCC. Various studies have demonstrated that GGT could induce DNA damage and regulate the cell cycle, highly correlating with tumor progression (33, 34). Platelets are small, nonnuclear fragments of blood cells, which are detached from bone marrow megakaryocytes. When blood vessels are damaged, platelets rapidly gather at the injury site and release platelet-activating factors to promote clot formation (35). It plays an active role in various stages of tumorigenesis, encompassing tumor growth, tumor cell extravasation, and metastasis. Moreover, their secretion of large quantities of microparticles and exosomes helps to effectively coordinate tumor-host crosstalk (36, 37).

Other clinical characteristics in the nomogram include age and hemoglobin. In particular, age is a recognized risk factor for the overall survival. Older patients with HCC generally had unfavorable prognoses due to poor baseline status, high mutation burden, rapid tumor progression, and co-morbidities (38). It is shown in some research that elderly patients exhibit diminished liver weight and portal blood flow rate, leading to weakened liver repairability and a poor prognosis (39). Hemoglobin, a special protein in red blood cells, is a vital carrier responsible for transporting oxygen (40, 41). It is crucial for maintaining normal oxygen supply in the body. The concentration of hemoglobin is the key factor in assessing respiratory health and detecting conditions. Clinical trials have revealed that a majority of cancer patients have low hemoglobin levels as a consequence of the disease. Specifically, reduced hemoglobin has a significant impact on the prognosis through several mechanisms, such as cellular compromise and impaired oxygenation (42).

There are some limitations that should be acknowledged in our study. Firstly, this study was conducted at a singular medical center, and the sample size was insufficient. Moreover, despite internal validation being undertaken, the absence of external validation remains as another notable limitation. Our future studies could benefit from multicenter collaborations to validate the nomogram across diverse patient populations and healthcare settings, enhancing its external validity. And then, the retrospective records of this study, which rely on historical patient information, lead to inevitable bias. This bias occurred because the study depended on existing data, which may exclude undocumented cases that were available for analysis. Finally, the population selected for this study only included HBV-related HCC patients with compensated cirrhosis. Thus, more studies are required to emerge with a solid foundation for the wider application of our nomogram.

Conclusions

In conclusion, we established and validated a nomogram model incorporating GPR, age, and hemoglobin for predicting the 3-, 5-,

and 8-year OS among HCC patients with compensated cirrhosis who underwent local ablation. This nomogram exhibited good predictive capability, which could be instrumental in postoperative surveillance and early intervention.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Beijing You'an Hospital affiliated with Capital Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this was a retrospective analysis of existing data.

Author contributions

WYQ: Data curation, Software, Writing – review & editing. JSL: Data curation, Software, Writing – original draft. PYW: Writing – original draft. YYZ: Conceptualization, Funding acquisition, Methodology, Supervision, Visualization, Writing – review & editing. RHJ: Conceptualization, Funding acquisition, Methodology, Supervision, Visualization, Writing – review & editing. JJL: Conceptualization, Funding acquisition, Methodology, Supervision, Visualization, Writing – review & editing.

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Conflict of 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1406764/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Flow chart of the patients included in the study.

SUPPLEMENTARY FIGURE 2
The ROC curve of GPR, age, hemoglobin, Fib-4, APRI, and the combination of GPR and NLR. GPR, gamma-glutamyl transpeptidase-to-platelet ratio; Fib-4, fibrosis 4 score; APRI, aspartate transaminase to platelet ratio index; NLR, neutrophil to lymphocyte ratio index.

SUPPLEMENTARY FIGURE 3
Kaplan-Meier curves of RFS for two risk groups classified by the nomogram in training and validation cohort. **(A)** training cohort; **(B)** validation cohort. RFS, recurrence-free survival.

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Efficacy and safety of variceal embolization for primary prophylaxis in cirrhosis patients with challenges in standard treatments: preliminary results

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Objectives: Nonselective beta blockers (NSBBs) or endoscopic therapies are currently recommended by guidelines for preventing the first variceal bleed in patients with high-risk varices. However, there is a lack of detailed treatment strategies for patients who are intolerant to both NSBBs and endoscopic approaches. Our study aimed to assess the efficacy and safety of variceal embolization as a primary prophylaxis method in cirrhosis patients who are not suitable candidates for NSBBs or endoscopic treatments.

Methods: The study included 43 cirrhotic patients with high-risk varices who were candidates for primary prophylaxis against variceal bleeding. These patients underwent variceal embolization at the Xijing Hospital between January 2020 and June 2022. The primary endpoint was the occurrence of bleeding from varices, and the secondary endpoints were the recurrence of varices and the emergence of complications.

Results: The procedure of variceal embolization had a success rate of 93.0% (40 out of 43 patients). Over a 2-year follow-up period, the rate of variceal bleeding was 11.6% (5 out of 43 patients), the recurrence rate of varices was 14.0% (6 out of 43 patients), and the rate of severe complications was limited to 2.3% (1 out of 43 patients).

Conclusion: Variceal embolization is a viable primary prophylactic intervention for cirrhotic patients who are at risk of variceal bleeding when standard treatments, such as NSBBs or endoscopic therapies, are difficult to perform.

KEYWORDS

variceal embolization, primary prophylaxis, cirrhosis, hypertension, portal, variceal bleeding

Introduction

Variceal bleeding is a serious complication of portal hypertension secondary to cirrhosis. At the point of diagnosis, approximately 50% of patients with cirrhosis are found to have esophageal and/or gastric varices (EGVs). Patients without EGV at diagnosis develop varices at an annual rate of approximately 8%, and patients with small EGV pose a 22% annual risk of progression to

medium or large varices. Additionally, 10–15% of patients with EGV experience their initial variceal bleeding each year, and the mortality rate for the first episode of variceal bleeding is high, with approximately 15% of patients dying from this initial bleeding (1, 2). Therefore, primary prophylaxis to prevent the first episode of variceal bleeding is essential in the management of cirrhosis.

Current guidelines recommend non-selective beta-blockers (NSBBs) as the first-line treatment for preventing the first variceal hemorrhage in patients with high-risk EGV. If NSBBs are contraindicated or not tolerated, endoscopic band ligation (EBL) is the preferred alternative for esophageal varices (EVs). For high-risk GVs, endoscopic cyanoacrylate injection (ECI) is recommended when NSBBs are not suitable (3–6). However, the guidelines currently lack detailed treatment strategies for patients who are unable to tolerate both NSBBs and endoscopic procedures.

Variceal embolization encompasses a range of interventional procedures aimed at occluding varicose veins. This approach is minimally invasive, technically straightforward, and has been confirmed to have efficacy and safety in both acute variceal bleeding treatment and secondary prophylaxis (7–9). Notably, in the treatment of GV, embolization with cyanoacrylate is superior to ECI (10). Given the efficacy and safety profile of variceal embolization, we hypothesize that it could also be a viable option for primary prophylaxis against variceal bleeding. This study aims to assess the effectiveness and safety of variceal embolization as a primary prophylactic intervention in cirrhosis patients who are not candidates for NSBBs and endoscopic treatments.

Methods

Study design

This was a single-arm retrospective observational study. It consecutively enrolled patients with cirrhosis and high-risk EGV who were admitted to Xijing Hospital from January 2020 to June 2022. Follow-up for the last patient extended beyond 6 months. Written informed consent was obtained from all patients for the use of their data in this research. The study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Air Force Medical University (approval number: KY20232008-C-1).

The inclusion criteria were as follows: (1) patients who are aged between 18 and 75 years; (2) patients with cirrhosis diagnosed by biopsy or a combination of medical history, etiology, physical examination, clinical presentation, biochemical testing, and imaging; (3) patients with high-risk EGV confirmed by endoscopic examination; (4) patients difficult to be treated with NSBBs and EBL/ECI as evaluated by two endoscopists; and (5) patients receiving variceal embolization with cyanoacrylate and/or coil for the prevention of EGV bleed. The exclusion criteria were as follows: patients with (1) a history of variceal bleeding; (2) hepatocellular carcinoma (HCC) beyond the Milan criteria; (3) malignant tumors excluding HCC; (4) main portal vein thrombus of over 50% or cavernous transformation of the portal vein; (5) recurrent or refractory ascites; (6) end-stage renal disease with renal replacement treatment; (7) cardiorespiratory failure; (8) human immunodeficiency virus infection or acquired immune deficiency syndrome; or (9) lack of baseline data and/or follow-up data.

Data collection and follow-up

The following data were collected for all patients: (1) baseline data including age, sex, etiology of liver disease, liver function, variceal type, and enhanced CT/MRI; (2) treatment information including access to the operation, embolization details, and operation-related complications; and (3) follow-up data including main symptoms, variceal bleeding, blood biochemistry, the changes of varices, and overall survival.

Endoscopic evaluations of varices were performed at 1, 3, and 6 months after the initial procedure and subsequently at 6-month intervals to monitor variceal changes. The study was concluded for each patient either upon the occurrence of an endpoint event, which was either variceal bleeding or recurrence, or after a minimum follow-up duration of 6 months post-embolization.

Variceal embolization with cyanoacrylate and steel coils

Our study utilized two approaches to variceal embolization: percutaneous transhepatic varices embolization (PTVE) and transjugular varices embolization (TJVE). PTVE involves accessing the varices via a percutaneous transhepatic route, known for its ease of operation. TJVE, alternatively, uses a transjugular intrahepatic route, which is preferred in patients with severe thrombocytopenia or significant ascites due to its reduced risk of abdominal hemorrhage. The criteria for selecting the approach were based on platelet counts and the presence of ascites: PTVE for patients with platelet counts above $50 \times 10^3/\mu L$ without ascites and TJVE for those with counts below $50\times 10^3/\mu L$ or with significant ascites.

The procedures were performed by Dr. Tie Jun, who possesses extensive experience with over a decade in conducting transjugular intrahepatic portosystemic shunt (TIPS) operations and has a professional record of conducting over 1,000 procedures. The TJVE procedure was conducted as follows: Initially, the femoral artery was accessed using the Seldinger technique, and then the superior mesenteric artery was selectively intubated for indirect portal vein angiography. Following this, the internal jugular vein was punctured, and a 0.035-inch guide wire (Terumo, Tokyo, Japan) was introduced through it into the inferior vena cava. Over this guide wire, the RUPS 100 puncture set (Cook, Chicago, United States) was advanced into the inferior vena cava. Subsequently, a portal vein branch was accessed from the right hepatic vein or the inferior vena cava, with placement confirmed by pushing a small amount of contrast agent. The guide wire was then maneuvered to the distal segment of the splenic or superior mesenteric vein for direct portal vein angiography, which facilitated the assessment of the varices in terms of location, morphology, size, and blood flow velocity. The 5F angiographic catheter was used to selectively intubate the varices. The varices were embolized with steel coils of appropriate diameter until the blood flow velocity of the varices slowed significantly. Then, a coaxial microcatheter (Boston Scientific Corporation, Massachusetts, United States) was inserted into the varices. The mixture of cyanoacrylate and iodide oil was slowly injected to make them flow slowly along the varicose veins and distribute in the reticular branches of the distal varicose veins until they were completely embolized. The ratio of iodide oil to cyanoacrylate was 3:1. For

varicose veins with diameters greater than 10 mm, the ratio of iodide oil to cyanoacrylate was reduced. After the embolization was completed, the end of the angiography catheter was placed at the splenic hilum, and direct portal vein angiography was performed again to confirm whether the varicose veins were completely embolized (Figure 1A).

The main PTVE procedure was as follows. The intrahepatic portal vein branch was punctured under ultrasound guidance. The guide wire was adjusted to the splenic vein or distal superior mesenteric vein, and the 5F angiographic catheter was advanced over the guide wire. Then, direct portal vein angiography was performed. The variceal embolization process was the same as that for TJVE. After variceal embolization, the puncture path was sealed with steel coils and cyanoacrylate (Figure 1B).

Definitions

High-risk EGV: grade I varices and red signs, grade 2–3 varices, and GVs larger than 10 mm in diameter (4, 5). EVs type 1 refers to grade I varices with positive red signs. EVs type 2 refers to grade 2–3 varices with or without positive red signs.

The types of high-risk EGVs are EV and GV. The GV was classified into gastroesophageal varices 1 (GOV1), gastroesophageal varices 2 (GOV2), isolated GV 1 (IGV1), and isolated GV 2 (IGV2), according to the Sarin classification (11).

Variceal bleeding: the presence of medium or large varices and red signs or active bleeding; the presence of blood in the stomach without any cause other than large varices (12, 13).

Variceal eradication: complete disappearance of varices or the presence of varices smaller than 5 mm in diameter and no red signs (14).

Variceal recurrence: the presence of varices larger than 5 mm in diameter after initial eradication (14).

Successful variceal embolization: direct portal angiography without visible varices after the operation and endoscopic variceal eradication at 1 month after variceal embolization (Figure 2).

Ascites occurrence: the new onset of any detectable ascites post-procedure in patients with no prior history of ascites before undergoing variceal embolization.

Worsening of ascites/hydrothorax: an increase in the ascites/hydrothorax volume from minimal to moderate or large, as determined by imaging or physical examination post-procedure.

Statistical analyses

All continuous variables are expressed as the median (range). Categorical variables are expressed as counts and percentages.

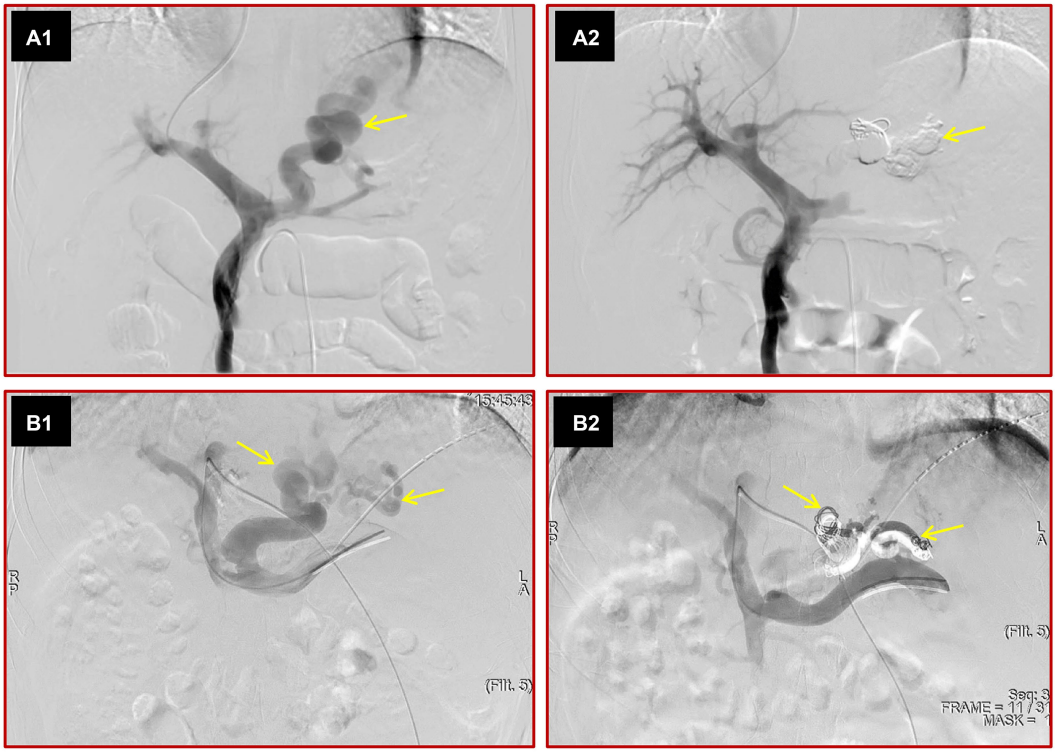

FIGURE 1
Images depict the two kinds of variceal embolization methods. The portal vein was punctured from the hepatic vein through internal jugular vein access, direct portal vein angiography was performed, and large varices (yellow arrow) were seen **(A1)**. After variceal embolization with cyanoacrylate and steel coils, the varices disappeared on direct portal angiography **(A2)**. The left portal vein was punctured by a percutaneous transhepatic approach, direct portal vein angiography was performed, and various large varices (yellow arrows) were observed **(B1)**. After variceal embolization with cyanoacrylate and steel coils, the varices were not seen **(B2)**.

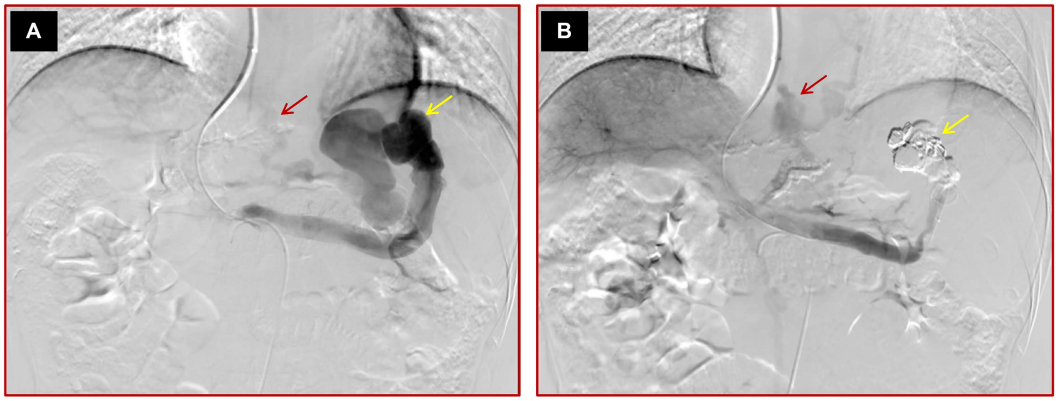

FIGURE 2
Images of a 45-year-old male cirrhotic patient with high-risk EV and IGV1 who failed variceal embolization. **(A)** The initial direct portal vein angiography reveals multiple varices and a prominent spontaneous splenorenal shunt, highlighted by yellow arrows. **(B)** Post-embolization angiography demonstrates that while the conspicuous spontaneous splenorenal shunt is no longer detectable, signifying partial procedural success, some varices persist, as indicated by a red arrow, suggesting incomplete occlusion.

Results

Patient characteristics

Between January 2020 and June 2022, a total of 73 consecutive patients underwent variceal embolization for high-risk EGV. However, 14 patients were excluded based on the exclusion criteria; 2 were over the age of 75 years, and 12 suffered from non-cirrhotic portal hypertension. An additional 16 patients were excluded for various reasons: 3 had a prior history of variceal bleeding, 10 patients had HCC who did not meet the Milan criteria, 1 was diagnosed with colon cancer, 1 was undergoing renal replacement therapy for end-stage renal disease, and 1 had a cavernous transformation of the portal vein. Consequently, 43 patients were eligible and enrolled in the study (Figure 3). The specific reasons for patients being unsuitable for NSBBs and endoscopic treatments are detailed in Table 1.

Of these participants, the median age was 54 years, with a range from 18 to 74 years. Male patients constituted 44.2% ($n=19$), and 48.8% ($n=21$) had hepatitis B virus-related cirrhosis. The median Child–Pugh score was 6, ranging from 5 to 12, and the median Model for End-Stage Liver Disease (MELD) score was 10, ranging from 4 to 22. Regarding varices types, 23.3% ($n=10$) of the patients exhibited EVs, while 76.7% ($n=33$) displayed GVs. Among the GV subgroup, 25.6% ($n=11$) had GOV1, 23.3% ($n=10$) had GOV2, 9.3% ($n=4$) had IGV1, and 18.6% ($n=8$) had a combination of more than one variceal type. Treatment modalities were nearly evenly split, with 51.2% ($n=22$) undergoing transjugular variceal embolization (TJVE) and 48.8% ($n=21$) receiving percutaneous transhepatic variceal embolization (PTVE). The follow-up period varied among participants, with the shortest being 77 days and the longest extending to 924 days. The median follow-up duration was 573 days. A comprehensive baseline characteristics of the patient cohort are detailed in Table 2.

Efficacy of variceal embolization

Out of 43 patients, 93.0% (40 patients) achieved successful embolization, as confirmed by the absence of visible varices on post-operative portal angiography. During the follow-up, five patients (11.6%) experienced variceal bleeding; these individuals were subsequently treated with TIPS therapy. The median interval from embolization to bleeding was 40 days, ranging from 3 to 454 days. Notably, bleeding occurred within 6 weeks for the three patients whose embolization was not successful, whereas it occurred at 250 days and 454 days for the two patients with initial successful procedures. This suggests that failed embolization may lead to an early increase in portal vein pressure and subsequent bleeding from residual varices. In contrast, no short-term bleeding was observed in patients with successful embolization. Over 2 years, the variceal bleeding rate remained at 11.6%. Additionally, 14.0% of patients experienced a recurrence of high-risk EGV, with a median time to recurrence of 195 days. Among the 13 patients with pre-existing hepatic ascites or hydrothorax, 30.8% experienced a worsening of these conditions, typically within 43 days. Conversely, 20.0% of patients without initial ascites and hydrothorax developed ascites, generally after a median time of 371 days. The study recorded a 7.0% mortality rate (three patients) during the follow-up period, but no deaths were directly attributed to variceal bleeding as per the data in Table 3.

Complications associated with variceal embolization

Abdominal pain was the most frequent complication, occurring in 51.2% of cases (22/43). Generally, the pain resolved within a week of symptomatic treatment. Nausea and vomiting were reported in 30.2% (13/43) of patients. Fever was present in 7.0% (3/43), while portal vein thrombosis was noted in one case (2.3%). There was one instance of abdominal hemorrhage (2.3%), which required hepatic artery embolization for management. Subcutaneous hematoma at the puncture site, either in the internal jugular vein or femoral artery, was observed in 4.7% (2/43) of the patients. These hematomas typically resolve with local compression between 2 and 4 weeks post-operation. Ectopic embolization of cyanoacrylate occurred in 4.7% (2/43) of patients due to large spontaneous portosystemic shunts. However, the embolization particles were small, and the scope of embolization was limited, resulting in no clinical symptoms, and consequently, no

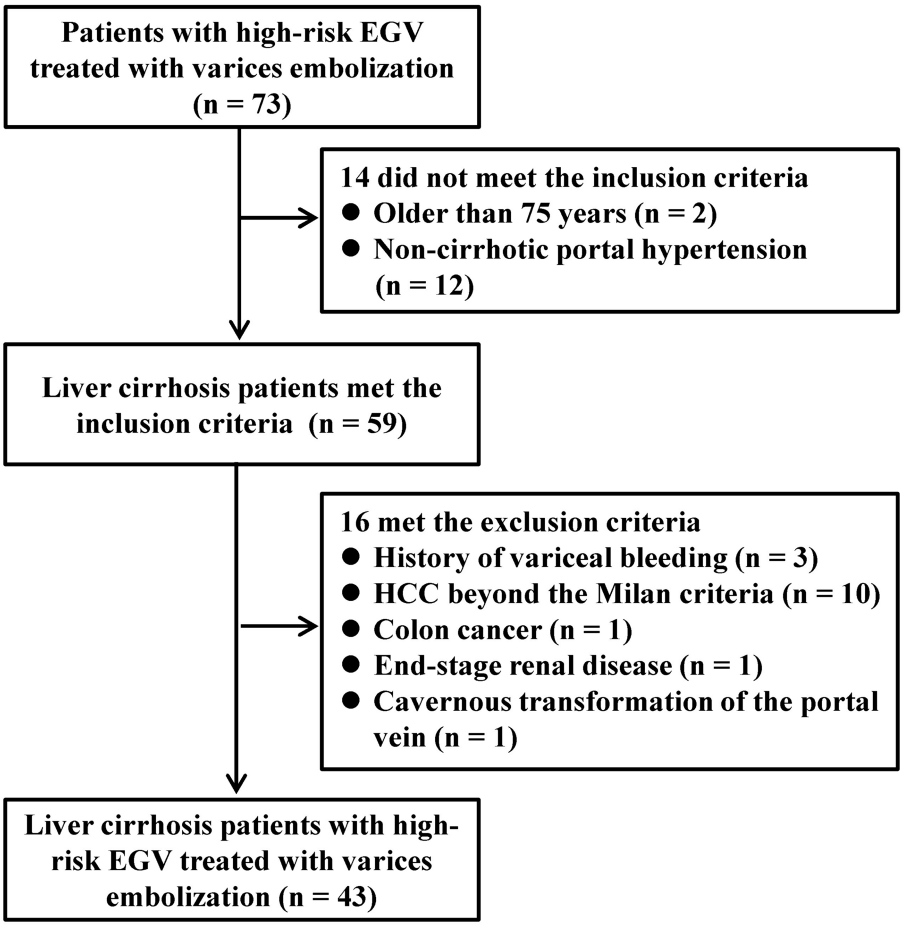

FIGURE 3
Flowchart of patient selection.

TABLE 1 Detailed reasons for exclusion from NSBBs and endoscopic treatment.

Reasons for exclusion from NSBBs	Number (*n* = 43)
History of bronchospasm	13
Second or third-degree atrioventricular block	2
Sick sinus syndrome	2
Resting heart rate below 50 beats per minute.	4
Heart failure or clinically significant hypotension	3
Peripheral vascular disease	1
Liver function classified as Child–Pugh class C	3
History of diabetic ketoacidosis	7
Significant adverse reactions to carvedilol	8
Reasons for exclusion from endoscopic treatment	
Severe coagulopathy	3
Severe thrombocytopenia ($<30 \times 10^9$/L)	6
Severe cardiopulmonary dysfunction	13
Varices with a diameter greater than 2 cm	21

NSBBs, Non-selective beta-blockers.

intervention was required for these cases, as shown in Table 4. There were no fatal complications reported. Overall, the rate of severe complications, such as abdominal hemorrhage, was low, at only 2.3% (1/43).

Discussion

Current guidelines recommend NSBBs or EBL/ECI for the prevention of initial variceal bleeding in patients with cirrhosis. However, these options are not viable for patients who are intolerant to both treatments. In this retrospective study, we assessed the effectiveness and safety of variceal embolization as primary prophylaxis in 43 patients with cirrhosis who were difficult to treat using NSBBs and EBL/ECI. The findings indicated a high success rate of 93.0% for variceal embolization. Over 2 years, the rate of variceal bleeding was 11.6%, and the recurrence of EGV was 14.0%. Importantly, there were no fatal complications associated with the procedure. This study is the first to demonstrate that variceal embolization can be a safe and effective primary prophylactic measure against variceal bleeding in patients who are not candidates for NSBBs and EBL/ECI.

TABLE 2 Baseline demographic and clinical characteristics.

Parameter	Value
Median (range) or absolute (percentage)	
Age (years)	54 (18–74)
Sex (Male)	19 (44.2%)
Etiology	
HBV	21 (48.8%)
HCV	3 (7.0%)
Others	19 (44.2%)
Liver function	
MELD scores	10 (4–22)
Child–Pugh scores	6 (5–12)
Child–Pugh class A/B/C	25/15/3
Compensation stage	25 (58.1%)
Type of varices	
Esophageal varices	10 (23.3%)
EV1	1 (2.3%)
EV2	9 (20.9%)
Gastric varices	33 (76.7%)
GOV1	11 (25.6%)
GOV2	10 (23.3%)
IGV1	4 (9.3%)
More than one variceal type	8 (18.6%)
Variceal diameter (mm)	15 (4–25)
Presence of a red sign	26 (60.5%)
Gastro-renal shunt	21 (48.8%)
Ascites/hepatic hydrothorax	13 (30.2%)
Hepatic encephalopathy	7 (16.3%)
Access to the operation	
Transjugular	22 (51.2%)
Transhepatic	21 (48.8%)
Median follow-up (days)	573 (77–924)

HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model of end-stage liver disease; EV1, esophageal varices type 1; EV2, esophageal varices type 2; GOV1, gastroesophageal varices type 1; GOV2, gastroesophageal varices type 2; IGV1, isolated gastric varices type 1.

TABLE 3 Efficacy of variceal embolization.

Parameter	Value
Successful embolization	40 (93.0%)
First variceal bleed	5 (11.6%)
Median time to first bleed	40 (3–454)
2-year bleeding rate	5 (11.6%)
High-risk EGV recurred	6 (14.0%)
Median time to variceal recurrence	195 (97–605)
2-year EGV recurrence rate	6 (14.0%)
Fresh ascites	6 (14.0%)
Median time to ascites occurrence	371 (257–478)
Hepatic ascites/hydrothorax at baseline	13 (30.2%)
Worsening of ascites/hydrothorax	4 (30.8%)
Median time to worsening of ascites	43 (31–57)
Mortality	3 (7.0%)
Bleeding mortality	0 (0.0%)

This study suggests that variceal embolization is an effective option for the primary prevention of variceal bleeding. For patients on NSBBs, a reduction in the risk of bleeding is only observed in those who exhibit a hepatic venous pressure gradient (HVPG) response. The HVPG response rate to NSBBs in patients with cirrhosis varies between 30 and 60% (15–17), implying that at least approximately 40% of patients may not benefit from NSBB therapy. Comparatively, the long-term variceal bleeding rate within 2 years for patients undergoing EBL spans from 8.5 to 23%, with an associated mortality rate of approximately 4.6% from variceal bleeding (18–20). Additionally, the actuarial probability of bleeding from GV over a median follow-up of 26 months was reported to be 13% in patients receiving ECI for primary prophylaxis (21). In contrast, the 2-year variceal bleeding rate in this study was 11.6% among patients receiving variceal embolization, with no occurrences of variceal bleeding-related mortality.

This study also demonstrated that variceal embolization is safe. Up to 20% of patients with cirrhosis are intolerant to NSBBs (22), with approximately 3.7% experiencing serious adverse reactions (23). Additionally, the use of NSBBs in patients with Child–Pugh class C liver function remains controversial. There is potential for lethal hemorrhage from recent post-procedure ulcers after EBL (2). ECI in patients with high-risk GV has 3% serious complications and 7% overall mortality (21). In this study, severe complications occurred in only 2.3% (1 out of 43) of the cases following variceal embolization, with no fatalities reported. These findings suggest that variceal embolization is comparable to the methods recommended by the current guidelines in terms of safety.

This study used an enhanced variceal embolization technique, contributing to its efficacy and safety. Variceal embolization encompasses all interventional procedures aimed at occluding varicose veins, primarily through retrograde or anterograde approaches. Retrograde procedures, such as balloon-occluded retrograde transvenous obliteration (BRTO), are limited to patients with spontaneous splenorenal shunts. In contrast, anterograde embolization, which includes balloon-occluded antegrade transvenous obliteration (BATO) and PTVE, applies to a broader range of varices. In this study, the anterograde embolization technique was selected for its versatility. We opted for a non-balloon-assisted embolization method, avoiding the complexities of maneuvering balloon catheters into tortuous varices, which can lead to procedural failure and increased complications associated with balloon catheter indwelling, as seen in classical BRTO. A variety of catheters, such as the Cobra, MIK, and microcatheters, were utilized for the successful catheterization of varices, achieving almost a 100% success rate. Instead of using sclerosing agents, which have been associated with serious complications such as hemolysis and renal impairment (24), this study used a combination of steel coils and cyanoacrylate tissue adhesives. This approach not only shortened the operation time but also minimized complications (25, 26). The steel coils reduced blood flow, while the cyanoacrylate ensured complete and reticular embolization, effectively preventing ectopic embolization without the need for a balloon catheter post-operation. Cyanoacrylate was injected into an extensive variceal network, targeting the lower esophageal, periesophageal, paraesophageal, gastric cardiac, and perforating veins. This comprehensive and occlusive embolization

TABLE 4 Complications.

Complications	Frequency n (%)
Non-operation-related complications	
Abdominal pain	22/43 (51.2%)
Nausea and vomiting	13/43 (30.2%)
Fever	3/43 (7.0%)
PVT	1/43 (2.3%)
Operation-related complications	
Abdominal hemorrhage	1/43 (2.3%)
Subcutaneous hematoma	2/43 (4.7%)
Ectopic embolism	2/43 (4.7%)

strategy significantly reduced the likelihood of a short-term recurrence of EGV.

This study is subject to certain limitations. First, the study is retrospective in nature even though the data were collected prospectively. The findings require validation through prospective, large-sample studies. Second, the determination of when endoscopic treatments were difficult was subjective. Since both EBL and ECI require specific expertise, and because the proficiency of endoscopists can vary widely, the decision to prevent variceal bleeding is often influenced by the level of available local expertise at a given center. To minimize these limitations, particularly those associated with technical proficiency and interpretive variability, decisions were made collaboratively by two experienced endoscopists. This approach aimed to ensure a more standardized assessment and reduce the potential bias in determining the suitability of endoscopic treatment options.

In conclusion, the results of this study indicate that variceal embolization is a viable and safe alternative to the established standard treatments for the primary prophylaxis of variceal bleeding. This technique offers a definitive treatment pathway for patients who are intolerant to NSBBs or endoscopic therapies.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Medical Ethics Committee of the First Affiliated Hospital of Air Force Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. XY: Methodology, Data curation, Resources, Validation, Visualization, Writing – review & editing. YZ: Investigation, Methodology, Resources, Validation, Writing – review & editing. KL: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – review & editing. XG: Resources, Writing – review & editing. NH: Data curation, Resources, Software, Validation, Visualization, Writing – review & editing. JN: Data curation, Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. JX: Resources, Validation, Visualization, Writing – review & editing. WW: Software, Validation, Writing – review & editing. YS: Software, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of 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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A clinical-radiomics nomogram for the prediction of the risk of upper gastrointestinal bleeding in patients with decompensated cirrhosis

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Objective: To develop a model that integrates radiomics features and clinical factors to predict upper gastrointestinal bleeding (UGIB) in patients with decompensated cirrhosis.

Methods: 104 decompensated cirrhosis patients with UGIB and 104 decompensated cirrhosis patients without UGIB were randomized according to a 7:3 ratio into a training cohort ($n = 145$) and a validation cohort ($n = 63$). Radiomics features of the abdominal skeletal muscle area (SMA) were extracted from the cross-sectional image at the largest level of the third lumbar vertebrae (L3) on the abdominal unenhanced multi-detector computer tomography (MDCT) images. Clinical-radiomics nomogram were constructed by combining a radiomics signature (Rad score) with clinical independent risk factors associated with UGIB. Nomogram performance was evaluated in calibration, discrimination, and clinical utility.

Results: The radiomics signature was built using 11 features. Plasma prothrombin time (PT), sarcopenia, and Rad score were independent predictors of the risk of UGIB in patients with decompensated cirrhosis. The clinical-radiomics nomogram performed well in both the training cohort (AUC, 0.902; 95% CI, 0.850–0.954) and the validation cohort (AUC, 0.858; 95% CI, 0.762–0.953) compared with the clinical factor model and the radiomics model and displayed excellent calibration in the training cohort. Decision curve analysis (DCA) demonstrated that the predictive efficacy of the clinical-radiomics nomogram model was superior to that of the clinical and radiomics model.

Conclusion: Clinical-radiomics nomogram that combines clinical factors and radiomics features has demonstrated favorable predictive effects in predicting the occurrence of UGIB in patients with decompensated cirrhosis. This helps in early diagnosis and treatment of the disease, warranting further exploration and research.

KEYWORDS

liver cirrhosis, upper gastrointestinal bleeding, sarcopenia, MDCT, radiomics, nomogram

1 Introduction

Cirrhotic patients often experience malnutrition due to reduced food intake, malabsorption, and decreased protein synthesis, leading to a decrease in both the quantity and quality of skeletal muscle (1, 2). Sarcopenia is a condition that results in decreased muscle mass and quality, and it is a common complication of cirrhosis (3). Cirrhotic patients with sarcopenia are at a higher risk of experiencing reduced quality of life, associated complications, and lower survival rates compared to cirrhotic patients without sarcopenia (3, 4). Sarcopenia can be used as a predictor of the occurrence and prognosis of complications in cirrhosis (4, 5).

As we know, patients with decompensated cirrhosis usually have clinical symptoms such as portal hypertension, ascites, esophagogastric fundal vein varices (GEVs), and splenomegaly. The presence of cirrhosis and ascites can increase the likelihood of intra-abdominal hypertension (IAH) (6). Elevated intra-abdominal pressure can cause abdominal muscle spasms, fatigue, and decreased anti-tension. Prolonged abdominal hypertension can cause degeneration and atrophy of the abdominal muscles. In patients with cirrhotic portal hypertension, elevated intra-abdominal pressure (IAP) may have deleterious effects on oesophageal variceal hemodynamics, significantly increasing variceal pressure and wall tension (7). In addition, decompensated cirrhotic patients with concomitant IAH and abdominal muscle weakness are at higher risk of developing umbilical or abdominal wall hernias (8). Based on the above reports, it seems that changes in abdominal muscles could be linked to the development and advancement of complications related to cirrhosis. Additionally, measuring the skeletal muscle at the L3 level may serve as an indicator of the patient's overall body mass and nutritional status in individuals with cirrhosis.

About 50% of cirrhotic patients have gastroesophageal varices (GEV), and 25–35% of those patients will experience upper gastrointestinal bleeding (UGIB) (9, 10). Liver cirrhosis complicated by UGIB is a dangerous and rapidly progressing condition that can cause severe bleeding, shock, and acute peripheral circulatory failure, with a high lethality rate (11). The gold standard for clinical assessment of UGIB and GEV is endoscopy (12). However, due to the endoscopy's invasive nature, some cirrhotic patients cannot tolerate this procedure because it may induce varicose vein bleeding (13). Therefore, simpler, non-invasive alternatives to endoscopy are needed to predict the risk of UGIB in patients with decompensated cirrhosis.

Current non-invasive methods for predicting UGIB include serological markers, imaging indicators, elastography and combinations of various indicators. Serological markers, such as von willebrand factor (vWF), vitro score, platelet count (PLT), and prothrombin time (PT), lack the desired sensitivity and specificity, requiring further validation for practice use (14–16). In addition, the measurement of the portal vein, splenic vein diameter, blood flow velocity, blood flow volume, and other abdominal ultrasound indicators for predicting oesophageal varices and bleeding risk can be easily influenced by the operator's own experience and subjectivity (17, 18). Transient elastography (TE) indirectly reflects the hepatic venous pressure gradient (HVPG) value by measuring liver stiffness to predict the degree of portal hypertension and the risk of bleeding (19), but the interference of ascites, obesity, gastrointestinal gas, and other factors may lead to errors in prediction.

MDCT is one of the routine investigations for cirrhosis, aiding in the diagnosis and evaluation of cirrhosis complications. Previous studies have analyzed quantitative CT indicators and radiomics of the liver, spleen, and esophagogastric fundal veins to predict UGIB risk in cirrhotic patients (20, 21). As far as I know, no studies have been conducted to investigate the relationship between quantitative CT indicators, radiomics of abdominal muscles, and the risk of UGIB in decompensated cirrhotic patients. Hence, the study aimed to create a non-invasive method based on MDCT to predict UGIB in decompensated cirrhotic patients by integrating clinical factors and radiomics features of abdominal muscles.

2 Materials and methods

2.1 Patients and data acquisition

The hospital ethics review board committee approved this retrospective study [Number 2022ER322-1], and the informed consent was waived. This study screened 208 patients with decompensated cirrhosis in our hospital from January 2019 to May 2023, based on inclusion and exclusion criteria. Criteria for inclusion: (1) age $\geq$ 18 years; (2) patients with decompensated cirrhosis, diagnostic criteria based on 2019 revised diagnostic and treatment guidelines for liver cirrhosis of the Chinese Medical Association, hepatology branch (22); (3) patients did not have upper gastrointestinal bleeding within 1 year prior to admission; (4) patients received endoscopy and whole abdomen MDCT scan after admission, and completion of a CT scan within a week before endoscopy; and (5) the relevant clinical information and laboratory tests were complete. Criteria for exclusion: (1) combined primary liver cancer or other malignant tumors; (2) patients have previously undergone any of the following: endoscopic variceal ligation or sclerosis, partial splenic artery embolization, splenectomy, or other surgery; (3) patients with hepatic encephalopathy; and (4) patients with poor image quality, imperfect relevant clinical information, and laboratory tests. See Figure 1 for the patient selection flowchart.

2.2 Patient clinical information

By reviewing the medical records of all patients, these clinical data including age, sex, body mass index (BMI), and routine blood and coagulation indexes within 24 h after admission, such as PLT, hemoglobin, total bilirubin, albumin, PT, international normalized ratio (INR), creatinine, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were reviewed and collected in medical records. Based on clinical signs and imaging examination results, ascites were graded into 3 grades according to the European Association for the Study of the Liver (EASL) criteria (23), grade 1: a small amount of ascites that can only be detected by ultrasonography or MDCT; grade 2: moderate amount of ascites with moderate and symmetrical abdominal distention; and grade 3: a large amount of ascites with significant abdominal distention. Liver function is graded

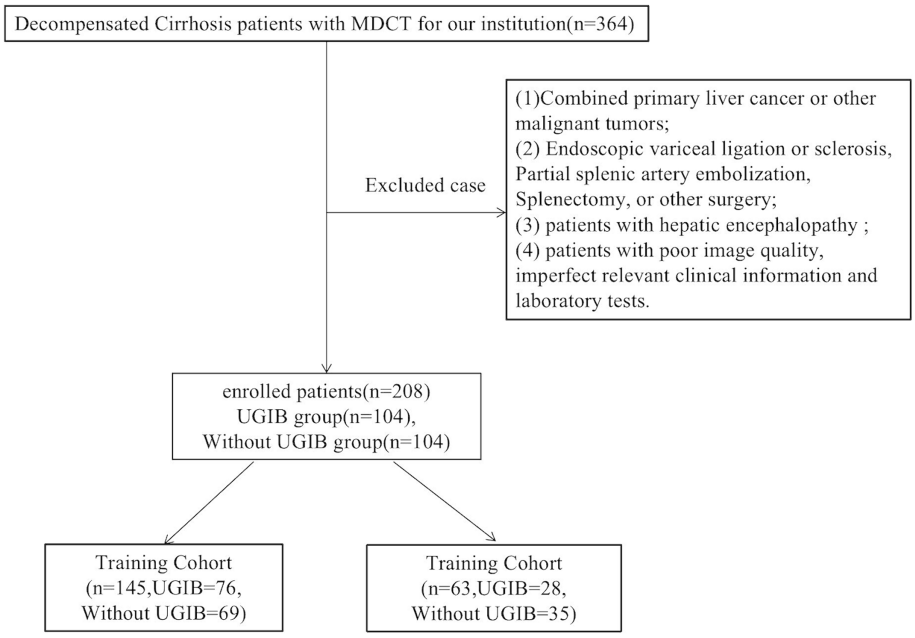

FIGURE 1
Flowchart of inclusion and exclusion procedures for this study.

based on the Child-Pugh score, which takes into account clinical features such as ascites and encephalopathy, as well as laboratory values such as serum albumin, bilirubin, and PLT (24).

2.3 Endoscopy

Endoscopy is used as the gold standard for UGIB and ruling out bleeding caused by ulcers. The criteria for bleeding in this study were based on one or more of the following signs: (1) active oozing or bleeding at the site of the varices, with no other bleeding sources during endoscope; and (2) finding a thrombus head on a visible variceal vein without finding a bleeding lesion elsewhere (12). Endoscopy was performed by an experienced gastroenterologist. All the patients who underwent endoscopy varices were classified as small varices<5 mm, and large varices>5 mm. Red color sign (RC) was defined that the surface of oesophageal varices showed red wale marking (RWM), cherry red spot (CRS), hematocystic spot(HS), and diffuse redness(DR) on endoscopy.

2.4 CT scan parameters and image acquisition

The scan was performed using a GE LightSpeed VCT 64-slice spiral CT, with the range from the diaphragm to the pubic symphysis. The scanning parameters are as follows: tube voltage of 120 Kv, tube current ranging from 250 to 300 mA, scan time of 0.5 s/360°, pitch of 1.0, acquisition slice thickness of 1.0 mm, reconstructed slice thickness of 5 mm, matrix size of 512 × 512. A nonionic iodinated contrast medium with an iodine concentration of 370 mg/mL (Yangzijiang, Jiangsu, China) was intravenously injected at a rate of 4 mL/s using a power injector with a dose of 2 mL/kg body weight, with an upper limit of 100 mL per patient. An abdominal pre-contrast CT scan was performed first, followed by two post-contrast CT scans during the arterial phase (25–30S) and the venous phase (45–50S).

On CT images, we measured the spleen diameter (SD) and spleen thickness (ST). The SD was defined as the longest diameter of the spleen at the central level of the splenic hilum (anteroposterior straight line). The ST was defined as the shortest diameter from the inner margin to the outer margin of the spleen at the central level of the splenic hilum.

2.5 The measurement of the abdominal skeletal muscle area and density, and subcutaneous fat area

The Slice-O-Matic software (5.2.1 version, https://tomovision.com/) was used to semi-automatically identify the entire abdominal wall muscles at the maximum level of the L3 according to the threshold of −29 to 150 HU, and the subcutaneous fat according to the threshold of-30 to-190 HU, respectively. After determining the internal and external contours of the muscles, they were separated from the subcutaneous fat and abdominal fat. Any misidentified areas in the images were corrected by manual adjustment. The subcutaneous fat area (SFA, cm^2), skeletal muscle area (SMA,cm^2), and skeletal muscle density (SMD, HU) of the abdomen were automatically

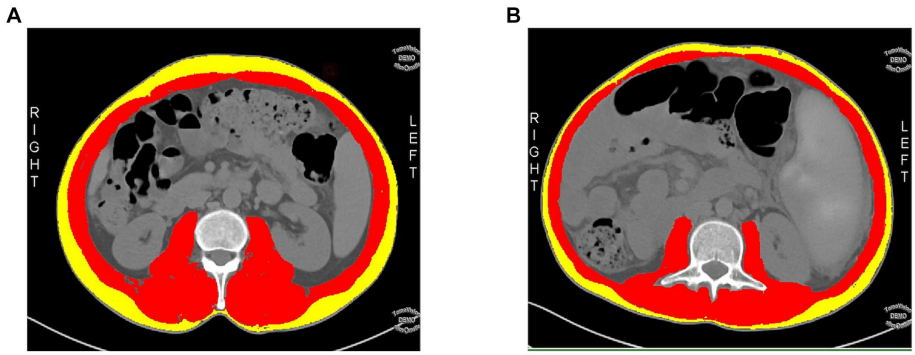

FIGURE 2
A cross-sectional abdominal skeletal muscle area (SMA, cm^2; red areas), surrounding subcutaneous fat area (SFA; yellow areas) and skeletal muscle density (SMD, HU) were measured on abdominal cross-sectional MDCT images at the maximum level of the third lumbar vertebra(L3) using sliceomatic software. **(A)** A 48-year-old male patient with a decompensated cirrhosis without upper gastrointestinal bleeding(UGIB), SMA = 148.9 cm^2, SFA = 68.09 cm^2, SMD = 47.99HU. **(B)** A 49-year-old male patient with decompensated cirrhotic patient with UGIB, SMA = 115 cm^2, SFA = 38.28 cm^2, SMD = 41.53HU.

calculated and obtained (25). For details, see Figure 2. This work was completed by radiologists (reader1and reader2) with experiences in diagnostic abdominal imaging, and the average of their two measurements was taken. The endoscopy results were not shared with the two radiologists.

The skeletal muscle index (SMI) is used for the evaluation of sarcopenia. The SMI was calculated using the formula SMI=SMA (cm^2)/height^2 (m^2). We used the diagnostic criteria for sarcopenia in the Chinese population based on SMI, as reported by Zeng et al. (26), men with an SMI of less than 44.77 cm^2/m^2 and women with an SMI of less than 32.50 cm^2/m^2 were defined as sarcopenia.

2.6 Feature extraction and selection of radiomics

The cross-section of abdominal muscles at the maximal level of the L3 was selected as the regions of interest (ROI). ROI was outlined semi-automatically using 3D slicer software (4.11.2 version, https://www.slicer.org/), and manually adjusted to guarantee utmost accuracy. Using R software (4.2.2 version, http://www.R-project.org), we extracted radiomics features from each ROI. For each patient's ROI, 1223 radiomics features describing the L3-skeletal muscle's internal and surface texture were extracted.

To analyze inter-and intra-observer reliability, 68 cases were selected randomly from the total sample. After 1 month, two radiologists segmented and extracted features from these images separately. An intraclass correlation coefficient(ICC) value above 0.75 was considered highly reproducible for reliability assessment, features with ICC values exceeded 0.75 were included in subsequent analysis (27).

The large number of redundant features obtained after feature extraction leads to overfitting and reduces the discriminative power of the model. LASSO regression allows active selection on large sets of multicollinear variables and uses collapsed cross-validation to select the most effective predictive features (28). Final filtered features were weighted using the LASSO algorithm to generate a Rad-score by linear combination, and then a radiomics model was built.

2.7 Radiomics nomogram construction

The Rad-scores and the clinical variables (clinical data and CT quantified features) were tested in univariate logistic regression analysis. All variables with $p < 0.05$ were entered into the multivariate logistic regression analysis. A radiomics nomogram was then constructed according to the multivariate logistic regression model.

2.8 Model performance assessment

Plotting and calculating receiver operating characteristic curves (ROC), accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and F1-score for each model to assess the generalization ability of the model. The area under the ROC curve (AUC) of the three models was compared using the Delong test. If the p-value is less than 0.05, it is considered to have statistical significance. Then, the nomogram was evaluated using calibration curves. Decision curve analysis (DCA) can assess the usability of a model and show the "net benefit" of a model (29). Therefore, we used DCA to analyze and compare the performance of the three models in terms of clinical utility.

2.9 Statistical analysis

The clinical data was analyzed using SPSS (version 27.0, IBM, Armonk, NY). Radiomics feature and model performance were analyzed using R. Continuous variables are expressed as mean ± standard deviation (SD), while categorical variables are expressed as numbers and percentages. Normal distribution of continuous parameters was compared using independent samples t-test, and non-normal distribution was compared using Mann–Whitney U test. Categorical parameters were compared using chi-squared test. Univariate analyses were conducted to identify risk factors associated with the development of UGIB in patients with decompensated cirrhosis. Significant indicators from the univariate analyses were included in multivariate logistic regression analyses. Results with $p < 0.05$ were considered statistically significant.

TABLE 1 Consistency within and between observers in terms of SMA and SFA.

Variables	ICCs	95%CI		*p*	ICCs	95%CI		*p*
		Lower limit	Upper limit			Lower limit	Upper limit	
SMA (cm^2)	0.984	0.977	0.988	<0.001	0.990	0.987	0.992	<0.001
SFA (cm^2)	0.916	0.890	0.936	<0.001	0.934	0.913	0.950	<0.001
SMD (HU)	0.945	0.926	0.959	<0.001	0.959	0.943	0.970	<0.001

SMA, skeletal muscle area; SFA, subcutaneous fat area; SMD, skeletal muscle density; ICCs, inter-and intra-group correlation coefficients; CI, confidence interval.

LASSO regression analyses of radiomics features were performed using the R package "glmnet." Nomograms and calibration curves were generated using the "rms" software package. Finally, the "dca.r" package is used to calculate the DCA.

3 Results

3.1 Clinical factors selection and construction of the clinical model

ICC results showed excellent consistency (all ICC > 0.75, $p < 0.001$) between radiologist 1 and radiologist 2 for intra-and interobserver measurements of SMA, SFA, and SMD values on MDCT (Table 1).

Table 2 showed the fundamental characteristics of the patients in the training ($n = 145$) and validation ($n = 63$) cohort. Univariate logistic regression showed that the Child-Pugh score grade, Albumin, PT, INR, PLT, AST, SD, SMA, SMD, and sarcopenia between decompensated cirrhotic patients with and without UGIB were significant differences in the training cohorts ($p < 0.05$), multivariate logistic regression analysis showed that sarcopenia and PT could be used as independent risk factors to predict UGIB in patients with decompensated cirrhosis ($p < 0.05$) (Figure 2; Table 3). The AUC for clinical factors was 0.822 (95% *CI* 0.753–0.891) in the training cohort and 0.756 (95% CI 0.634–0.877) in the validation cohort (Table 4).

3.2 Radiomics model establishment

Of the 1,223 radiomics features extracted, 1,082 features were proved to have good inter-and intra-observer agreement with ICCs >0.75. 88 radiomics features showing significant differences between decompensated cirrhotic patients with and without UGIB ($p < 0.05$) were incorporated into the LASSO logistic regression to determine the best valuable features (Figure 3). Eventually, 11 different features were screened to form the radiomics signature (Figure 3; Table 5). Radiomics features showed good predictive accuracy, with an AUC of 0.830 (95% *CI*, 0.762–0.897) in the training cohort and 0.765 (95% *CI*, 0.644–0.886) in the validation cohort (Table 4).

3.3 The clinical-radiomics nomogram model building and assessment of the performance of different model

The diagnostic performances of the three models were showed in Table 4. The ROC curves of the three models were displayed in Figure 4. It was found that the clinical-radiomics nomogram model demonstrated superior diagnostic performance than the radiomics features (AUC: 0.902 vs. 0.830, $p = 0.003$) and the clinical factors (AUC: 0.902 vs. 0.822, $p = 0.005$), but the radiomics signature's diagnostic performance was not different significantly from the clinical factors (AUC: 0.830 vs. 0.822, $p = 0.86$), in the prediction of UGIB in decompensated cirrhotic patients (Figure 4).

Calibration curves showed better calibration in the training cohort and validation cohort (Figure 5). Results from the DCA suggest that the clinical-radiomics nomogram model provides a greater net benefit for clinical decision-making than the radiomics and clinical models in the training cohort (Figure 5).

4 Discussion

Our study constructed and verified a clinical-radiomics nomogram model to predict UGIB in patients with decompensated cirrhosis based on MDCT images of the L3 skeletal muscles. The clinical-radiomics nomogram, which combines radiomics features and clinical factors, demonstrated excellent diagnostic performance in predicting UGIB of decompensated cirrhotic patients.

Sarcopenia is prevalent in patients with liver cirrhosis. Patients with decompensated cirrhosis exhibit a notably elevated occurrence of sarcopenia compared to those with compensated cirrhosis (3). Sarcopenia is strongly associated with complications of liver cirrhosis, such as ascites, oesophageal varices, and hepatic encephalopathy (3–5, 26). However, few studies have reported the correlation between sarcopenia and upper gastrointestinal bleeding in cirrhosis. Topan et al. (30) and Aldo et al. (31) have shown that cirrhotic patients with sarcopenia have a higher incidence of oesophageal varices and variceal bleeding compared to those without sarcopenia. A study by Zeng et al. (26) showed that patients with cirrhosis combined with sarcopenia had a higher incidence of UGIB during the 2-year follow-up period compared to patients without sarcopenia. The results of the above studies are consistent with the results of our study. In our study, sarcopenia was strongly associated with UGIB. Decompensated cirrhotic patients with combined sarcopenia have a 5–6 times higher risk of UGIB compared to those without sarcopenia.

The abdominal SMD and SMA at the maximum level of L3 on MDCT can indirectly reflect the skeletal muscle mass of the whole body, reduced SMD and SMA imply an increased proportion of intermuscular fat and muscular atrophy. EbadiM's study showed that a reduced abdominal SMD at the maximum level of L3 is negatively correlated with clinical outcomes and strongly associated with complications of portal hypertension in cirrhotic patients (32). Our study found that the abdominal SMA and SMD, although markedly

TABLE 2 Baseline characteristics of decompensated cirrhotic patients with and without UGIB in the training and validation cohorts.

Variables	Training Cohort (*n* = 145)		*p*	Validation Cohort (*n* = 63)		*p*
	UGIB (*n* = 76)	Without UGIB (*n* = 69)		UGIB (*n* = 28)	Without UGIB (*n* = 35)	
Age(y), mean ± SD	57.3 ± 12.27	55.59 ± 10.83	0.377	57.61 ± 12.84	56.2 ± 10.19	0.629
Sex, male, *n* (%)	50 (65.8)	39 (56.5)	0.252	13 (46.4)	29 (82.9)	0.002
BMI (kg/m2)	22.49 (20.79, 25.08)	23.44 (21.07, 25.16)	0.402	22.33 (20.35, 25.76)	23.44 (21.16, 25.34)	0.59
Total Bilirubin (μmol/L)	28.35 (17.83, 50.5)	33 (17.95, 47.85)	0.954	24.05 (14.85, 40.93)	20.1 (13.9, 50.6)	0.879
Albumin(g/L)	30.44 ± 4.31	33.85 ± 5.74	<0.001	29.1 ± 4.53	34.34 ± 6.09	<0.001
ALT(U/L)	27.5 (18.3, 53.9)	35 (23, 53)	0.17	20.5 (13, 27.5)	27 (20, 55)	0.015
AST (U/L)	40.5 (26, 67)	52 (35.5, 91)	0.03	30 (20.5, 43.25)	34 (23, 72)	0.171
Creatinine (μmol/L)	69.85 (56.75, 79.48)	59.8 (51.4, 73.8)	0.016	60.3 (47.15, 75.85)	63 (51.5, 74.8)	0.52
PT(s)	18.05 (16.9, 19.4)	15.60 (14.2, 17.6)	<0.001	18 (16.68, 18.9)	15.4 (13, 17.5)	<0.001
INR (%)	1.45 (1.29, 1.67)	1.36 (1.2, 1.54)	0.005	1.43 (1.36, 1.59)	1.36 (1.2, 1.49)	0.062
Hemoglobin (g/L)	81.5 (65, 100)	108 (86, 121)	<0.001	71.5 (58.25, 84)	111 (80, 128)	<0.001
PLT (10^9/L)	72 (60.25, 83)	83 (71, 98.5)	<0.001	75.5 (57.25, 83.75)	88 (79, 100)	0.01
Child-Pugh *n* (%)			0.001			0.001
A	5 (6.6)	19 (27.5)		0	14 (40)	
B	42 (55.3)	38 (55.1)		18 (64.3)	14 (40)	
C	29 (38.2)	12 (17.4)		10 (35.7)	7 (20)	
Endoscopy						
Large varices (*n*,%)	62 (81.6%)	40 (58%)	0.002	23 (82.1)	19 (54.3)	0.031
Small varices (*n*,%)	14 (18.4%)	29 (42%)		5 (17.9)	16 (45.7)	
Red (+)	61 (80.3)	24 (34.8)	<0.001	23 (82.1)	15 (39.5)	0.002
MDCT						
SMA (cm^2)	106.08 ± 20.64	118.7 ± 26.4	0.002	96.92 ± 17.97	122.79 ± 22.62	<0.001
SFA (cm^2)	73.99 (39.36, 132.35)	84 (43.56, 156.85)	0.346	78.53 (33.04, 133.2)	73.91 (34.66, 114.5)	0.825
SMD(HU)	36.27 ± 7.96	40 ± 5.8	0.002	34.67 ± 8.28	40.36 ± 6.79	0.004
SMI	39.51 (35.59, 44.05)	44.12 (38.92, 52.83)	<0.001	38.27 (34.33, 42.89)	44.92 (40.46, 49.22)	<0.001
Sarcopenia, *n* (%)	47 (61.8)	15 (21.7)	<0.001	17 (60.7)	11 (31.4)	0.02
SD (mm)	15.14 ± 2.12	14.3 ± 2.72	0.047	15.96 ± 2.26	14.43 ± 2.22	0.09
ST (mm)	5.62 ± 1.23	5.19 ± 1.22	0.036	5.92 ± 1.05	5.33 ± 1.13	0.035

UGIB, upper gastrointestinal bleeding; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; INR, international normalized ratio; PLT, platelet count; SMA, skeletal muscle area; SFA, subcutaneous fat area; SMD, skeletal muscle density; SMI, skeletal muscle index; SD, spleen diameter; ST, spleen thickness.

TABLE 3 Univariate and multivariate logistic regression analysis of patients with decompensated cirrhosis combine with UGIB in the training cohorts.

	Univariate logistic regression		Multivariate logistic regression	
	OR (95%CI)	*p*	OR (95%CI)	*p*
Albumin(g/L)	0.869 (0.806–0.937)	<0.001		
PT(s)	1.379 (1.187–1.602)	<0.001	1.538 (1.198–1.974)	0.001
INR (%)	4.950 (1.501–16.331)	0.009		
PLT	0.971 (0.954–0.988)	0.001		
Child-Pugh, *n* (%)	1.439 (1.197–1.730)	<0.001		
B	4.2 (1.429–12.348)	0.009		
C	9.183 (2.786–30.275)	<0.001		
SMA (cm^2)	0.977 (0.963–0.992)	0.002		

(Continued)

TABLE 3 (Continued)

	Univariate logistic regression		Multivariate logistic regression	
	OR (95%CI)	*p*	OR (95%CI)	*p*
SMD(HU)	0.925 (0.88–0.973)	0.003		
Sarcopenia, *n* (%)	5.834 (2.795–12.178)	<0.001	5.555 (2.037–15.147)	0.001
SD (mm)	1.338 (1.016–1.763)	0.038		
Rad score	2.718 (1.929–3.828)	<0.001	3.024 (1.953–4.681)	<0.001

UGIB, upper gastrointestinal bleeding; PT, prothrombin time; PLT, platelet count; SMA, skeletal muscle area; SMD, skeletal muscle density; SD, spleen diameter; OR, odds ratio.

TABLE 4 The AUC of radiomics model, clinical model, and nomogram model for predicting UGIB of the decompensated cirrhosis patients in the training and validation cohorts.

	AUC (95%CI)	Accuracy, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %	F1, %
Training cohort							
Radiomics model	0.830 (0.762–0.897)	77.9	80.3	75.4	78.2	77.6	79.2
Clinical model	0.822 (0.753–0.891)	74.5	73.7	75.4	76.7	72.2	75.2
Nomogram model	0.902 (0.850–0.954)	82.1	85.5	78.3	81.3	83.1	83.3
Validation cohort							
Radiomics model	0.765 (0.644–0.886)	68.3	81.8	53.3	65.9	72.7	73
Clinical model	0.756 (0.634–0.877)	66.7	60.6	73.3	71.4	62.9	65.6
Nomogram model	0.858 (0.762–0.953)	79.4	75.8	83.3	83.3	75.8	79.4

AUC, the area under the curve; PPV, positive predictive value; NPV, negative predictive value.

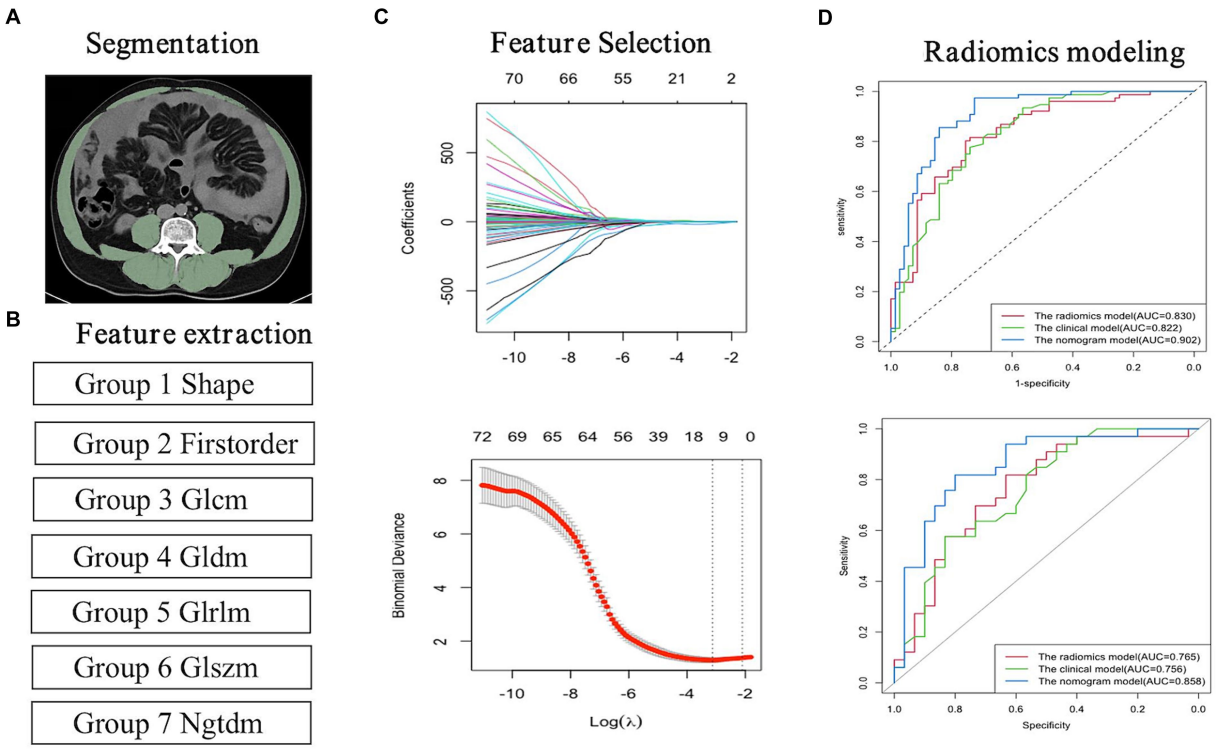

FIGURE 3
Flowchart for the radiomics analysis. **(A)** Image segmentation; **(B)** Feature extraction; **(C)** Feature selection and model building. **(D)** Radiomics model building.

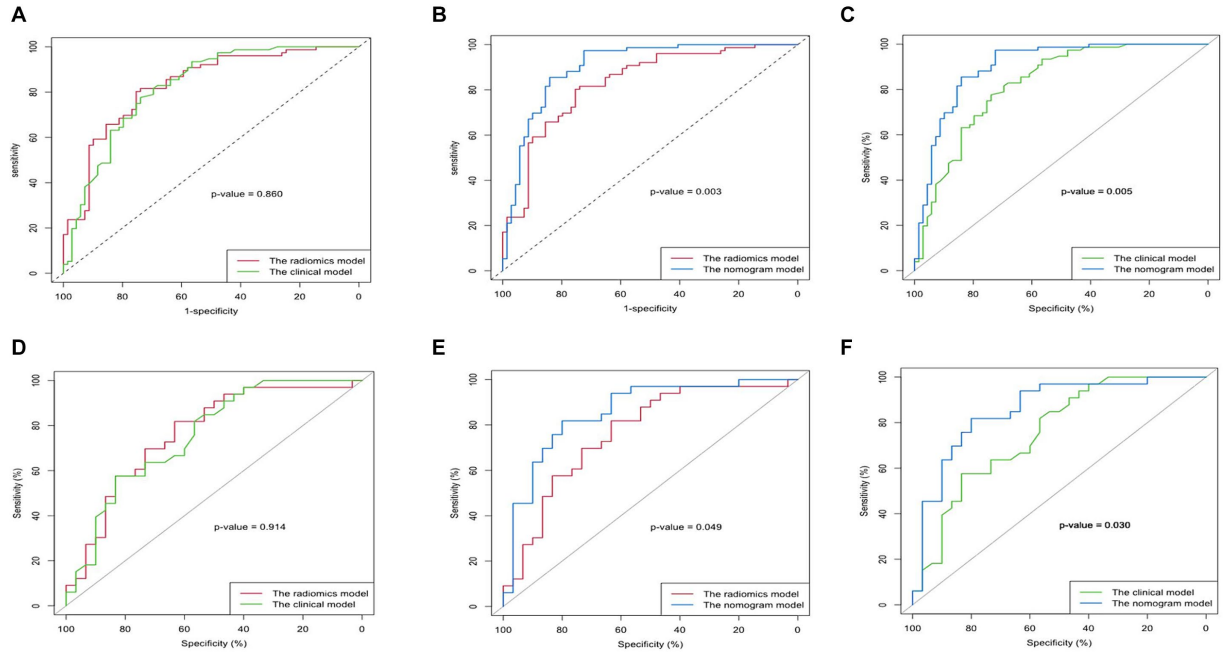

FIGURE 4
Comparison of the AUC of the clinical model, radiomics model, and nomogram model in predicting upper gastrointestinal bleeding (UGIB) of the decompensated cirrhosis patients [**(A–C)** Training set; **(D–F)** Validation set]. The nomogram model had better diagnostic performance than the radiomics model ($p < 0.05$) and the clinical model ($p < 0.05$), but the radiomics signature's diagnostic performance did not differ significantly from that of the clinical factors ($p > 0.05$) in both training and validation cohort.

TABLE 5 **Information on radiomics features after dimensionality reduction and feature selection by LASSO regression.**

3rd lumbar vertebra level muscles on MDCT			
NO.	Radiomics features	NO.	Radiomics features
N5	Shap (Maximum2DDiameterColumn)	N680	Firstorder (Skewness)
N83	Glrlm (RunVariance)	N932	Glszm (SizeZoneNonUniformity)
N193	Glszm (ZoneEntropy)	N1009	Glrlm (RunEntropy)
N366	Glszm (GrayLevelNonUniformity)	N1106	Glrlm (RunVariance)
N494	Firstorder (Skewness)	N1123	Glszm (ZoneEntropy)
N671	Firstorder (Kurtosis)		

LASSO, least absolute shrinkage and selection operator; MDCT, multi-detector computer tomography.

lower in decompensated cirrhotic patients with UGIB than those without UGIB, could not be used as independent hazard factors for forecasting UGIB in patients with decompensated cirrhosis. The reasons may be as follows: due to malnutrition and metabolic factors, the abdominal skeletal muscle in patients with cirrhosis develops fat deposition and atrophy at the same time, and single abdominal SMD and SMA cannot fully represent the pathological changes of skeletal muscle.

Liver cirrhosis in the decompensated phase is primarily characterized by long-term liver function damage, leading to decreased hepatic synthetic capacity and coagulation dysfunction (33–35). Our study found that some laboratory indicators reflecting liver reserve function status were associated with UGIB in patients with decompensated cirrhosis. This conforms to the pattern of disease progression, the more severe the liver function damage, the higher the risk of UGIB. Among these laboratory indicators, only PT could be an independent risk factor for predicting the risk of UGIB in patients with decompensated cirrhosis. The reason may be that PT is the most sensitive and widely used screening test for external coagulation.

With the progression of liver cirrhosis, the spleen becomes enlarged due to tissue hyperplasia, fibrosis, and portal congestion. The size of the spleen may be related to UGIB in patients with liver cirrhosis. In our study, the SD and ST showed a significant difference between patients with and without UGIB in the training cohort. The ST showed a significant difference, and the SD did not show a significant difference between patients with and without UGIB in the validation cohort. The univariate and multivariate analysis results of the training cohort showed that only ST was a risk factor for UGIB, however, it cannot be used as an independent risk factor for UGIB in patients with decompensated cirrhosis. The reason may be that

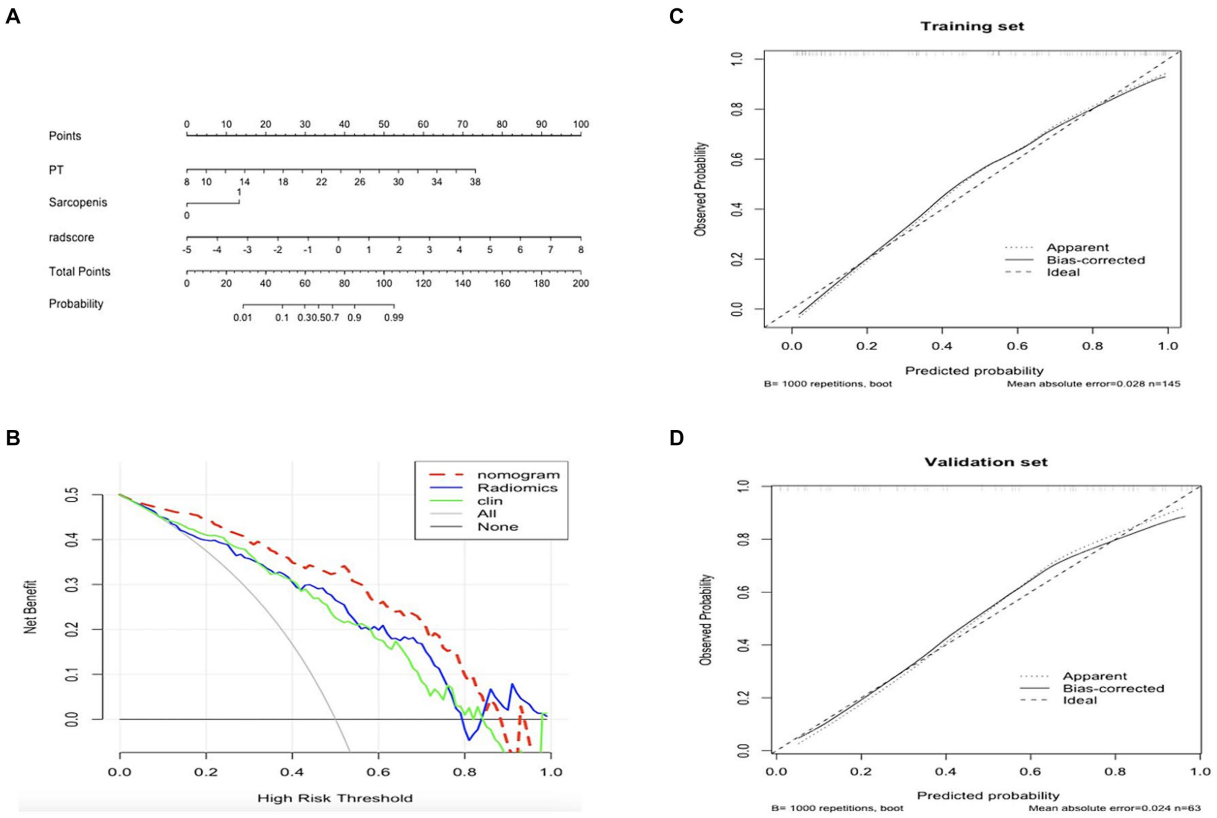

FIGURE 5
Plotting nomograms, clinical decision curves, and calibration curves to assess the predictive performance of the model. **(A)** The developed nomogram is based on the clinical-radiomics prediction model to predict the risk of upper gastrointestinal bleeding(UGIB) in patients with decompensated cirrhosis. Sarcopenia:1, non-sarcopenia:0. **(B)** Decision curve analysis of the three models in the training group. The light grey line assumes that all patients have the possibility of concomitant UGIB. The black horizontal line assumes that no patients have UGIB. X-axis represents the threshold probability. Y-axis measures the net gain. The blue line represents the radiological model. The green line represents the clinical model. Red line represents the combined model. **(C,D)** Calibration curves for the nomogram in the training and validation cohorts. The curve indicates that the net benefit of the nomogram is better than the other models when the threshold is within the range of 0.05–0.85 in the training cohort. The closer the ideal line fit to the apparent line, the greater the prediction accuracy of the nomogram.

individuals can have variations in the shape, size, and function of their spleen.

Radiomics is a non-invasive image analysis technique that employs high flux throughput feature extraction algorithms to quantitatively assess the distribution characteristics of grey levels and pixels in CT images, thereby revealing differences between individuals that cannot be identified by the human eye (36). We chose MDCT images of skeletal muscles at the level of the L3 vertebrae for feature extraction and combined the radiomics features with clinical features to establish a clinical-radiomics nomogram model. Radiomics can identify muscle features and tissue heterogeneity that are difficult to access through visual assessment, aiding in the early detection of muscle loss and mass loss during disease progression (37). In our study, the nomogram model showed better diagnostic and predictive ability than radiomics models and clinical models alone. The incorporation of both radiomics and clinical data may contribute to the excellent performance of the nomogram model. Such an approach allows for direct consideration of disease status and provides a greater advantage than the traditional MDCT image based on the SMA and SMD to assess the muscle features, resulting in superior model performance. In addition, DCA also validated that a nomogram model based on skeletal muscle mass analysis had more net benefit than clinical and radiomics models in predicting UGIB in decompensated cirrhosis.

There are several shortcomings in our study. First, we used a single-center, small-sample for our study, which may have been a source of bias. Therefore, future studies should consider multi-center studies with a larger sample to ensure more accurate results. Second, the muscle imaging histology model in this study was built based on 2D images, not 3D images. However, the imaging histology prediction model based on 2D images has shown some promising results. Additionally, the time spent on feature extraction and prediction model building was relatively short, making it more convenient and faster than the imaging histology processing of 3D images. Last, diagnostic accuracy in the training cohort in our study is usually overestimated. Therefore, prospective external validation is needed in future studies.

To sum up, the clinical-radiomics model was found to be more accurate in predicting the occurrence of UGIB in decompensated cirrhosis compared to individual clinical or radiomics models. This is valuable for the diagnosis of UGIB in patients with decompensated cirrhosis and could potentially complement the gold standard of endoscopy. Additionally, it offers new insights for evaluating the risk of UGIB in decompensated cirrhotic patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Medical Ethics Committee of Affiliated Hospital of North Sichuan Medical College. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

ZL: Writing – original draft. QH: Writing – original draft. XY: Writing – review & editing. TZ: Writing – review & editing. XL: Writing – review & editing. YL: Writing – review & editing. WT: Writing – original draft, Writing – review & editing. SP: Writing – review & editing.

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Conflict of 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.

Publisher's note

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Development and validation of a prognostic score for TIPS placement in patients with viral hepatitis cirrhosis-related portal hypertension: a multi-center retrospective study

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Introduction: There is no established scoring model focused on viral hepatitis patients to predict the prognosis after transjugular intrahepatic portosystemic shunt (TIPS). We aimed to develop and validate a novel model based on the largest cohort for better prediction of both short-term (1 year) and long-term (3 years) postoperative prognoses after TIPS in viral hepatitis cirrhosis-related portal hypertension patients.

Methods: A total of 925 viral hepatitis cirrhosis-related portal hypertension patients who underwent TIPS from nine hospitals were divided into the training and external validation cohorts. A novel Viral-associated Index of Post-TIPS score (VIPs) model was developed after performing Cox regression analysis. The VIPs model was compared to five previous models, namely, Child–Pugh, MELD, ALBI, CCG, and FIPS. Furthermore, X-tile software was used to stratify patients into low-, medium-, and high-risk groups.

Results: The VIPs model included age, ascites, albumin, prothrombin time, total bilirubin, and sodium for post-TIPS prognosis prediction. The model demonstrated satisfying predictive efficiency in both discrimination and calibration, with an area under the curve of 0.781/0.774 (1 year/3 years) in the training cohort and 0.771/0.775 (1 year/3 years) in the external validation cohort, respectively.

Discussion: We first developed and externally validated a novel VIPs model for better prediction of both short-term and long-term postoperative prognoses after TIPS in Chinese patients with viral hepatitis cirrhosis-related portal hypertension.

KEYWORDS
viral hepatitis, cirrhosis, portal hypertension, prognosis, mortality, model

1 Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is a recommended microinvasive treatment for complications caused by cirrhosis-related portal hypertension, such as esophagogastric variceal bleeding and refractory ascites (1–4). However, TIPS might increase the incidence rate of liver cirrhosis complications including hepatic encephalopathy and acute liver failure, which result in worse prognosis and quality of life (5, 6). Therefore, patient selection is particularly important before TIPS implantation.

The non-invasive method is an effective and promising way to predict the prognosis after TIPS. To date, several non-invasive clinical models were used for TIPS prognosis prediction, such as Child–Turcotte–Pugh (CTP) score (7), Model for End-Stage Liver Disease (MELD) score (8), albumin–bilirubin (ALBI) score (9), CLIF Consortium Acute Decompensation score (CLIF-C AD) (10), and Freiburg index of post-TIPS survival (FIPS) score (11). However, the models including CTP, MELD, ALBI, and CLIF-C AD were not constructed based on the TIPS population, and they were commonly used to predict short-term mortality rates in patients with end-stage liver disease or hepatocellular carcinoma. The FIPS score was the latest model for TIPS prognosis prediction based on the TIPS population, while its predictive ability remains to be further explored, especially in the Chinese cohort. FIPS, similar to models mentioned above, was based on Western cirrhosis cohorts and might not be suitable for the Chinese population, because cirrhosis in Western countries was most commonly caused by alcohol-related liver disease and non-alcoholic fatty liver disease (NAFLD), while cirrhosis in China is most commonly caused by viral hepatitis (HBV and HCV). Furthermore, our previous research and Han's cohort showed that the FIPS score might not be better than the CTP score in the Chinese population (12).

Viral hepatitis (HBV and HCV) was the main cause of cirrhosis in the Chinese population, accounting for approximately 79% (13). However, there was a lack of an appropriate scoring model for TIPS postoperative survival prediction in those patients. The purpose of this study was to first develop and externally validate a novel model for better prediction of both short-term (1 year) and long-term (3 years) postoperative prognoses after TIPS in patients with viral hepatitis cirrhosis-related portal hypertension. Moreover, our model was developed in the southwest (eight centers) and externally validated in the northeastern (one center) population of China, which was more representative and showed stable predictive ability in Chinese cohorts.

Abbreviations: Alb, Albumin; ALBI, Albumin–bilirubin; AUC, Area under the curve; CCG-AVB-TE, The Chinese Collaboration Group on the Acute Variceal Bleeding and Predicting the Treatment Effect; CLIF-C AD, CLIF Consortium Acute Decompensation; CTP, Child–Turcotte–Pugh; DCA, Decision curve analysis; FIPS, Freiburg index of post-TIPS survival; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HE, Hepatic encephalopathy; INR, International normalized ratio; MELD, Model for End-Stage Liver Disease; Na, Sodium; NAFLD, Non-alcoholic fatty liver disease; OS, Overall survival; PT, Prothrombin time; ROC, Receiver operating characteristic; TBIL, Total bilirubin; TIPS, Transjugular intrahepatic portosystemic shunt; VIPs, Viral-associated Index of Post-TIPS score.

2 Materials and methods

2.1 Study population

The ethical committees of all participating hospitals approved the research protocol. All research studies were conducted in accordance with both the Declaration of Helsinki. Written consent was given by all patients. This study was conducted among patients with viral hepatitis cirrhosis-related portal hypertension who underwent TIPS placement. A retrospective analysis of clinical data was conducted among patients who underwent TIPS placement in nine tertiary hospitals from May 2011 to September 2022. The follow-up period ended on 30 September 2023 or until the patient's death. The patients from Beijing Shijitan Hospital who met the criteria were included in the validation cohort, and patients from the remaining eight centers were included in the training cohort for model construction. All patients received oral antiviral therapy, and follow-up revealed that HBV DNA levels or HCV RNA levels were below the detection limit. This article was written according to the TRIPOD guideline (14). The inclusion criteria for this study were as follows: (1) patients with viral hepatitis-related cirrhosis (based on clinical features, laboratory and imaging tests, or liver biopsy) who underwent TIPS placement and (2) patients aged between 18 and 80 years old. The exclusion criteria were as follows: (1) patients who had liver cirrhosis due to other causes; (2) patients who had previously received devascularization or portosystemic shunts; (3) patients who had hepatocellular carcinoma or other malignant tumors; (4) patients who had non-cirrhotic portal hypertension; and (5) patients who had severe organ dysfunction such as congestive heart failure, severe valvular heart insufficiency, and a creatinine level of >442 μmol/L.

2.2 Outcomes

The main endpoint of the study was all-cause mortality during the follow-up period of 1 or 3 years after TIPS placement.

2.3 Predictive factors and data collection

Since our goal was to develop a score that predicts postoperative survival based on preoperative clinical data, the predictive factors were limited to variables collected within 3 days prior to TIPS placement. Specific information included basic patient information, clinical characteristics, and laboratory tests, as shown in Table 1.

TABLE 1 Baseline characteristics of the study patients in the training cohort and the validation cohort.

Variables	Training cohort, $n = 709$	Validation cohort, $n = 216$	p
Age (years)	49 ± 10	52 ± 11	0.001
Sex, *n* (%)			0.549
Men	534 [75.3]	167 [77.3]	
Women	175 [24.7]	49 [22.7]	
Indications for TIPS, *n* (%)			0.750
Variceal bleeding	662 [93.4]	203 [94]	
Ascites	47 [6.6]	13 [6]	
TIPS stent, *n* (%)			0.000
Covered stent	623 [87.9]	214 [99.1]	
Bare stent	86 [12.1]	2 [0.9]	
Ascites, *n* (%)			0.075
None	275 [38.8]	85 [39.4]	
Moderate	270 [38.1]	53 [24.5]	
Massive	164 [23.1]	78 [36.1]	
WBC (10^9/L)	3.16 (2.14–4.79)	2.97 (1.77–4.2)	0.017
Hb (g/L)	85 (71–103)	92 (79–115)	0.000
PLT (10^9/L)	54 (39–80)	75 (49–121)	0.000
ALT (U/L)	25 (17–37)	20 (15–27)	0.000
AST(U/L)	32 (24–44)	29 (21–35)	0.000
Alb (g/L)	34.7 ± 5.9	36 ± 5	0.001
INR	1.29 (1.17–1.46)	1.31 (1.19–1.43)	0.977
TBil (μmol/L)	20.3 (13.7–29.8)	21.5 (15.8–31.8)	0.015
Scr (μmol/L)	69 (58.1–81.3)	64 (55–76)	0.002
Na (mmol/L)	139.4 (137.2–141.0)	140 (138–142)	0.001
Child–Pugh score	7 (6–8)	7 (6–8)	0.689
MELD score	11 (9–14)	11 (9–13)	0.084
ALBI score	−2.08 ± 0.56	−2.15 ± 0.46	0.047
FIPS score	−1.03 (−1.47–−0.60)	−1.11 (−1.57–−0.51)	0.508
CCG-AVB-TEP1 score	−0.67 (−0.93–−0.36)	−0.71 (−0.94–−0.37)	0.438
Follow-up time(d)	1,027 (605–1,522)	1,268 (1137–1,494)	0.000

Mean ± standard deviation for normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and numbers [proportions, %] for categorical variables.
Hb, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Alb, albumin; INR, international normalized ratio; TBil, total bilirubin; Scr, serum creatinine; MELD, Model for End-Stage Liver Disease; ALBI, albumin–bilirubin; FIPS, Freiburg index of post-TIPS survival; CCG-AVB-TEP1, Chinese Collaboration Group on the Acute Variceal Bleeding score and Predicting the Treatment Effect.

2.4 Sample size calculation

The sample size was calculated using the method proposed by Richard D. Riley et al. (15). To develop a multivariate clinical prediction model, seven predictor parameters were included in the final model, with an adjusted R-squared of 0.1, shrinkage of 10%, and the 1-year mortality rate (outcome event) of 13%. Based on these assumptions, the minimum sample size required for model development is 595 patients with 78 outcome events. In this study, a total of 925 patients were finally enrolled, including 112 patients with outcome events.

2.5 Statistical analysis

All statistical analyses were performed using SPSS (version 26.0) or R (version 4.3.1), with the following packages: pmsampsize, car, survival, plyr, forestplot, ggplot2, survminer, rms, pROC, ggDCA, nomogramEx, nomogramFormula, and MASS. Statistical significance was set at $p < 0.05$ (two-sided). Normally distributed variables are expressed as the mean ± standard deviation and were compared using an independent-samples *t*-test. Non-normally distributed variables are expressed as medians and interquartile ranges and were compared using the Mann–Whitney rank-sum test. Categorical variables are expressed as numbers (proportions, %) and were compared using the $\chi 2$ test.

2.6 Prediction of the survival probabilities in patients under TIPS placement

Univariate Cox regression analysis was used to identify factors significantly associated with survival after TIPS placement, and variables with a *p*-value of <0.05 in the univariate analysis were included in subsequent multivariate analysis. Multivariate analysis used backward stepwise regression to select the prediction model with the minimum Akaike information criterion. In the final model, the prognostic score for each individual was calculated, and a nomogram was developed to calculate the survival prediction probabilities for 1 and 3 years.

The performance of the model was evaluated and validated through Harrell's C-statistic (C-index) (16) and calibration plot (17). Decision curve analysis (DCA) was used to assess the clinical utility of the model, which quantifies the net benefit at different threshold probabilities (18). The performance of the new model was compared to the Child–Pugh score, MELD score, ALBI score, FIPS score, and the Chinese Collaboration Group on the Acute Variceal Bleeding and Predicting the Treatment Effect (CCG-AVB-TEP1) model (19). The bootstrap method was used with 1,000 iterations to provide an unbiased estimate of the model's performance as the C-index. For external validation, the prognostic score for each individual in the validation cohort was calculated using the formula developed in the training cohort. The external validity was assessed by calculating the C-index and calibration plot and compared with other scoring models. X-tile software (20) was used to determine the optimal cutoff value for prognostic scoring, and a log-rank test was performed to assess whether there were differences among the risk groups and to distinguish the low-risk, medium-risk, and high-risk populations. The performance of the prognostic score in subgroups was assessed according to the etiology [hepatitis B virus (HBV) vs. hepatitis C virus (HCV)].

2.7 Score calculation

The Child–Pugh score included five parameters: total bilirubin, albumin, prothrombin time, ascites, and hepatic encephalopathy. The

final score was obtained by summing up the scores of each parameter. The formula for the MELD score is $3.8 \times \ln$ [(TBIL, μmol/L) ÷ 17.1] + $11.2 \times \ln$ (INR) + $9.6 \times \ln$ [(creatinine, μmol/L) ÷ 88.4] + $6.4 \times$ etiology (cholestasis or alcohol 0, others 1). The formula for the ALBI score is $0.66 \times \lg$ (TBIL, μmol/L) − $0.085 \times$ (albumin, g/L). The formula for the FIPS score is $1.43 \times \lg$ (TBIL, μmol/L) − $1.71 \times 1/$ (creatinine, mg/dL) + $0.02 \times$ (age, years) − $0.02 \times$ (albumin, g/L). The formula for the CCG-AVB-TEP1 score is $10 \times [0.0289 \times$ (age, years) − $0.0525 \times$ (albumin, g/L) + $0.3334 \times$ Ln (bilirubin, mg/dl) + $1.7631 \times$ Ln (INR) + $0.3373 \times$ Ln (WBC, 10^9/L) + $0.4509 \times$ Ln (creatinine, mg/dl) − $0.0294 \times$ (sodium, mmol/L) + 8] × 0.056838484–3.1231513.

3 Results

3.1 Baseline characteristics of patients and outcomes

A total of 2051 patients underwent TIPS placement at the centers. To develop a survival prediction model for TIPS placement, 1,126 patients who did not meet the inclusion criteria were excluded, and 925 patients were included in the subsequent model development and validation. The training cohort included 709 patients, while the validation cohort included 216 patients (Figure 1). The baseline characteristics of the two cohorts are shown in Table 1.

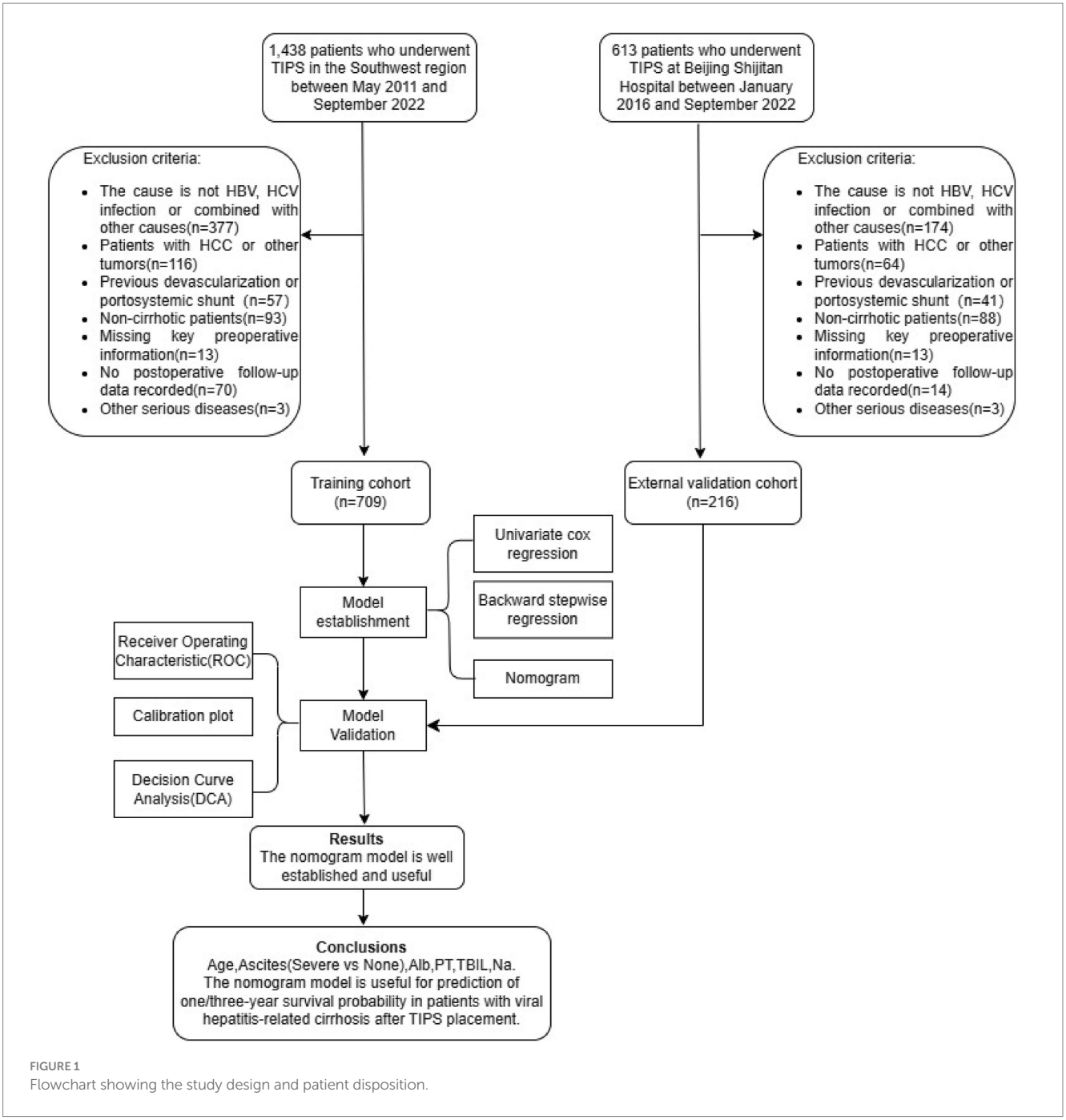

FIGURE 1
Flowchart showing the study design and patient disposition.

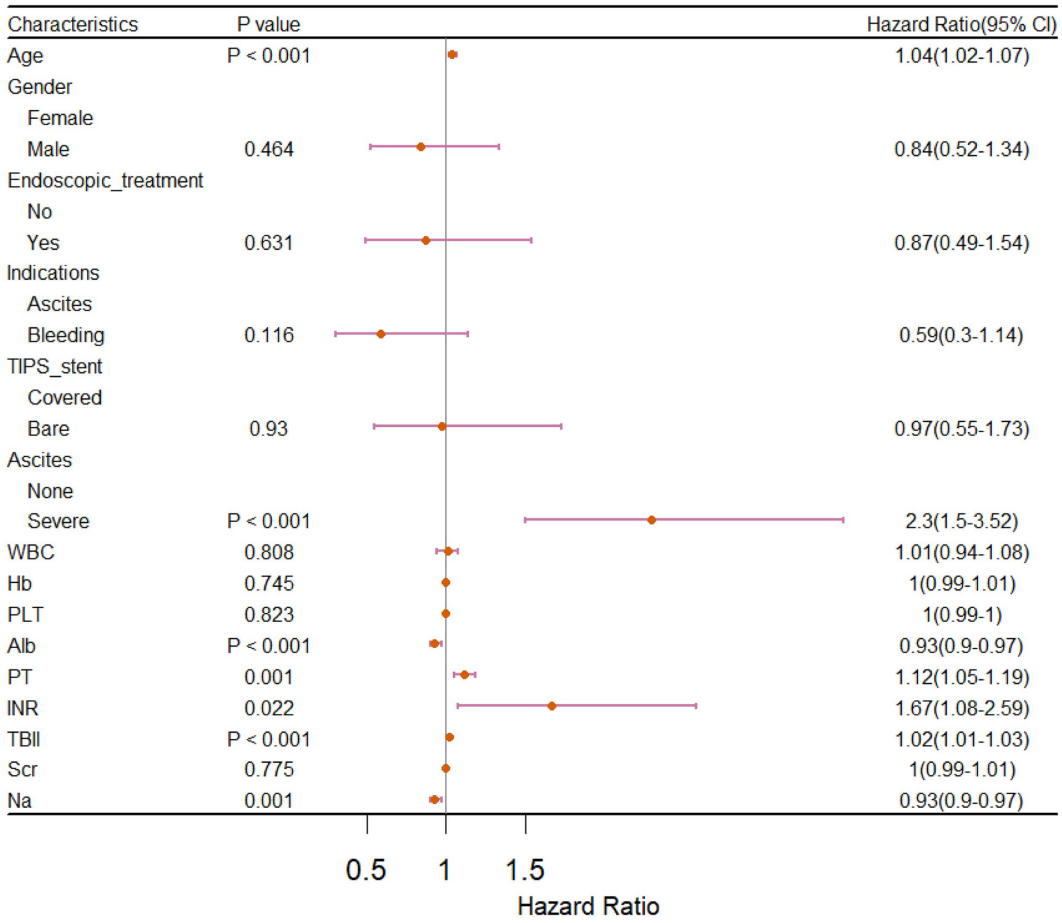

FIGURE 2
Forest plot of univariate Cox regression analysis for prognostic factors in patients who received TIPS.

3.2 Model development

The univariate Cox regression analysis of the training cohort showed that age, ascites, albumin, prothrombin time (PT), international normalized ratio (INR), total bilirubin (TBIL), and sodium ($p < 0.05$) were important risk factors for survival after TIPS placement (Figure 2). A backward stepwise regression method was used to develop a model with the selected variables, and the final multivariate model included age, ascites, albumin, PT, TBIL, and sodium (Na). Based on the final model, a risk score was developed and named the Viral-associated Index of Post-TIPS score (VIPs). The calculation formula for the risk score is as follows:

VIPs = 1.19 × age+9.01× ascites +1.9 × PT + 0.5 × TBil − 1.12 × Alb − 1.09 × Na + 181.62[age, years; PT, s; TBIL, μmol/L; Alb, g/L; Na, mmol/L; ascites: none = 0, severe (moderate or large ascites with moderately symmetrical abdominal distention or have significant abdominal distension) = 1].

We also developed a nomogram based on the final model to estimate the survival prediction probabilities for 1 and 3 years (Figure 3).

3.3 Model performance evaluation and internal validation

The discrimination of the VIP score was evaluated by calculating the area under the receiver operating characteristic (ROC) curve. The area under the curve (AUC) of the VIP score for 1- and 3-year survival prediction in the training cohort was 0.781 and 0.774, respectively (Figures 4A,B). The calibration plot showed that the VIP score was well-calibrated at 1-year and 3-year survival (Figures 5A,B). DCA of the VIP score demonstrated a higher net benefit than the other score (Figure 6A). We performed internal validation using a bootstrap method with 1,000 iterations to provide an unbiased estimate of the VIP score performance as the C-index. The results showed that the VIP score for survival in the training cohort was 0.733, which was significantly better than the C-indices of the Child–Pugh score (0.672; $p < 0.001$), the MELD score (0.601, $p < 0.001$), the ALBI score (0.658, $p < 0.001$), the CCG-AVB-TEP1 score (0.701, $p < 0.001$), and the FIPS score (0.652, $p < 0.001$) (Table 2).

3.4 External validation of the VIP score and subgroup analysis

In the external validation cohort, the VIP score also demonstrated excellent discriminative ability. This cohort had the largest C-index (0.869) compared to other scores (Table 2). The AUCs of the VIP score for 1- and 3-year survival prediction in the external validation cohort were 0.771 and 0.775, respectively (Figures 4C,D). DCA of the VIP score demonstrated a higher net benefit than the other scores in

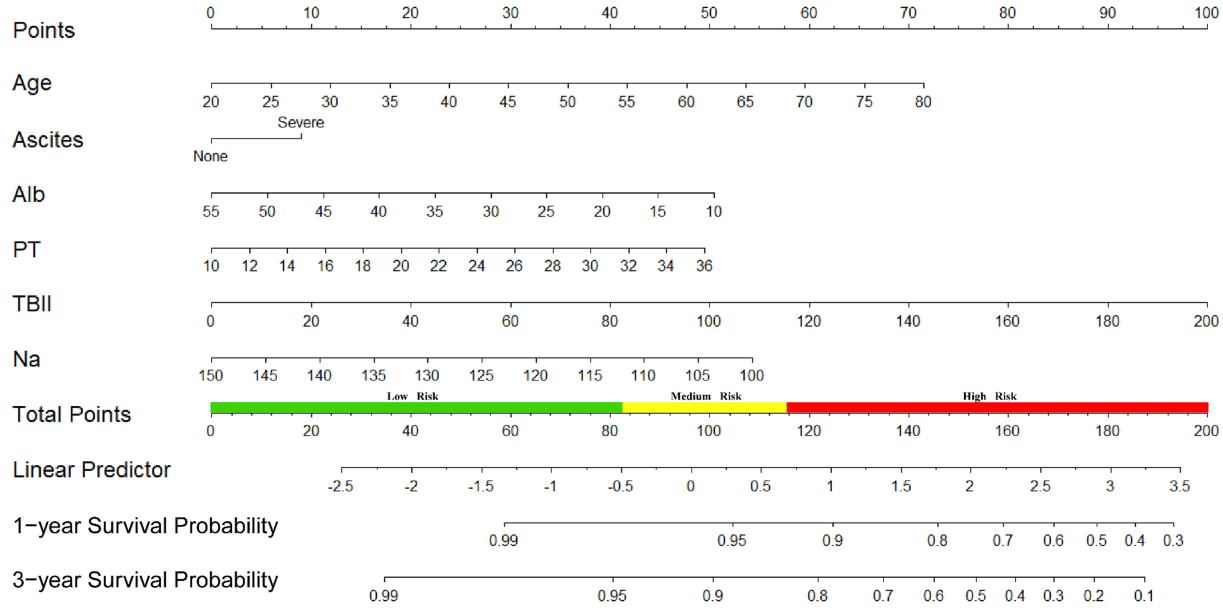

FIGURE 3
Nomogram to predict survival after TIPS.

the external validation cohort (Figure 6B). Similarly, the VIP score had good calibration at 1 year and 3 years (Figures 5C,D). In subgroup analysis, the VIP score showed fair to excellent performance for 1- and 3-year survival prediction in the HBV and HCV cohorts, which was superior to other scores (Figures 7A,B).

3.5 Risk stratification based on the VIP score

X-tile software generated two optimal cutoff values (83 and 115), which were used to divide the entire cohort into three risk groups: low risk (score < 83), medium risk (score 83–115), and high risk (score > 115). The 3-year cumulative mortality rates for the low-, medium-, and high-risk groups were estimated to be 34.5, 40.4, and 51.5% in the entire cohort, respectively. The Kaplan–Meier curve showed that, among the three risk groups, higher risk was associated with lower the overall survival (OS) (Figure 8, entire cohort, $\chi 2 = 86.37$, $p < 0.001$). Therefore, the VIP score could effectively stratify the risk of patients with viral hepatitis cirrhosis-related portal hypertension treated with TIPS placement.

4 Discussion

In China, the most common causes of liver cirrhosis are chronic HBV and HCV infections (21). Due to variations in healthcare resources and economic levels, the management of these patients differs from that in Western countries. Furthermore, liver transplants are relatively difficult to obtain in China. Therefore, TIPS is one of the major options for the treatment of complications associated with portal hypertension in cirrhosis. The prognosis of post-TIPS is usually based on the clinical characteristics of patients before TIPS placement. The non-invasive method is an effective and promising way to predict the prognosis after TIPS. However, there is no established scoring model focused on HBV and HCV patients to predict the survival of post-TIPS patients. In this study, we developed and externally validated a novel model to predict post-TIPS survival based on HBV and HCV Chinese patients. The performance of the model is good in terms of calibration and clinical benefit indicators.

In this multi-center retrospective study, we developed a simple score composed of six variables (age, ascites, albumin, PT, TBIL, and sodium) to predict the 1-year and 3-year survival of TIPS treatment for patients with viral hepatitis cirrhosis-related portal hypertension. According to the latest research, Han and Zhao conducted two models to predict post-TIPS prognosis based on Chinese cohorts. The CCG-AVB-TEP1 model proposed by Han (19) was based on non-TIPS cohorts (cirrhosis-related AVB patients who were treated with endoscopy plus drugs) and validated by a small sample of preemptive-TIPS cohorts. The model ^{MT} proposed by Zhao (22) did not analyze the etiology distinction. In addition, both models were used for predicting short-term survival after TIPS placement. Our study has several advantages: (1) The six variables were objective indicators that can be easily acquired. (2) This study was conducted based on the largest cohort of HBV and HCV-related cirrhosis patients who received TIPS implantation in China, which could make our results more representative and reliable. (3) The existing scores are mainly applicable to short-term prediction (time less than 1 year) after TIPS placement, while our developed score extends the prediction time to 3 years after TIPS and achieves good prediction performance. (4) There were major differences in economic levels and medical resources between the southwest and northeast in China. Our study was a multi-center effort that first developed a robust model based on the data from eight centers in

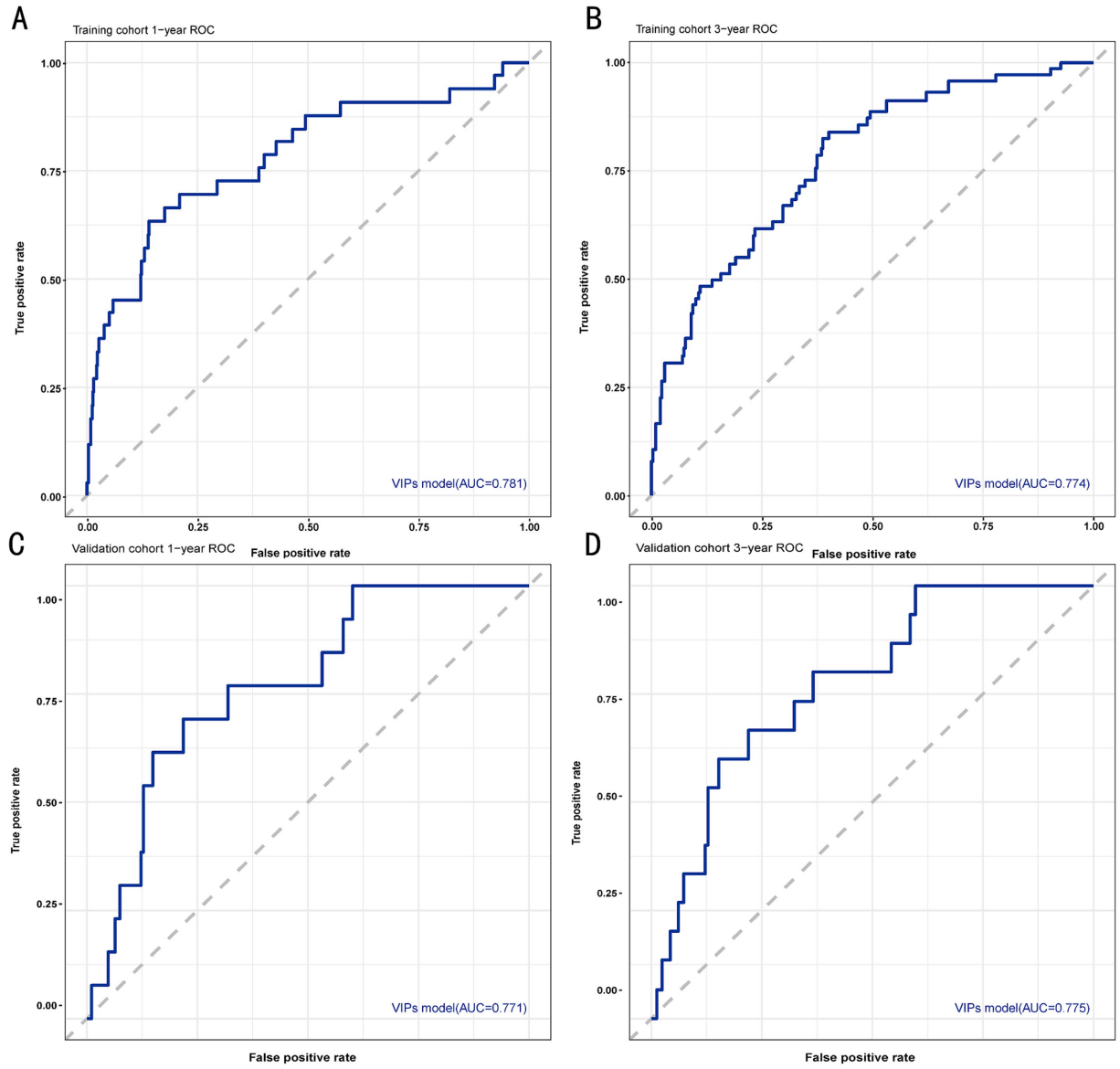

FIGURE 4
ROC curves for 1- and 3-year survival prediction of the VIP score model. **(A)** ROC curve for 1-year survival prediction using the training cohort. **(B)** ROC curve for 3-year survival prediction using the training cohort. **(C)** ROC curve for 1-year survival prediction using the validation cohort. **(D)** ROC curve for 3-year survival prediction using the validation cohort. The VIP score model showed excellent predictive value.

the southwest of China. We then externally validated this model using data from a center in the northeast of China, where it also demonstrated good performance. This suggests that our model is both representative and consistently reliable across different Chinese cohorts.

This study first constructed a model including these six variables, especially for the prediction of post-TIPS prognosis in HBV and HCV-related cirrhosis patients. According to previous studies, HBV and HCV-related cirrhosis patients exhibit worse liver function and renal function and more serious portal hypertension (23–25). Therefore, these six variables might be more suitable for the prediction of post-TIPS prognosis in HBV and HCV-related cirrhosis patients. Although hepatic encephalopathy (HE) is a proven prognostic factor for TIPS, we did not take HE as a screening variable because the diagnosis of HE is mainly based on clinical manifestations according to the subjective experience of the doctor, which cannot be easily uniformed in each center. Moreover, minimal hepatic encephalopathy cannot be diagnosed in a timely manner. This change improved the stability and ability of our model compared to the classic CTP score. Interestingly, we found that creatinine was not an independent prognostic factor, which is why those scoring models containing creatinine, such as the MELD, CCG, and FIPS scores, proved to be suboptimal in assessing prognosis. This may be because esophageal variceal bleeding was the main indicator for TIPS in our study, while refractory ascites accounted for only 6.6% of the cases. Patients with variceal bleeding exhibited an earlier stage of cirrhosis than patients with refractory ascites. This is the reason why fewer

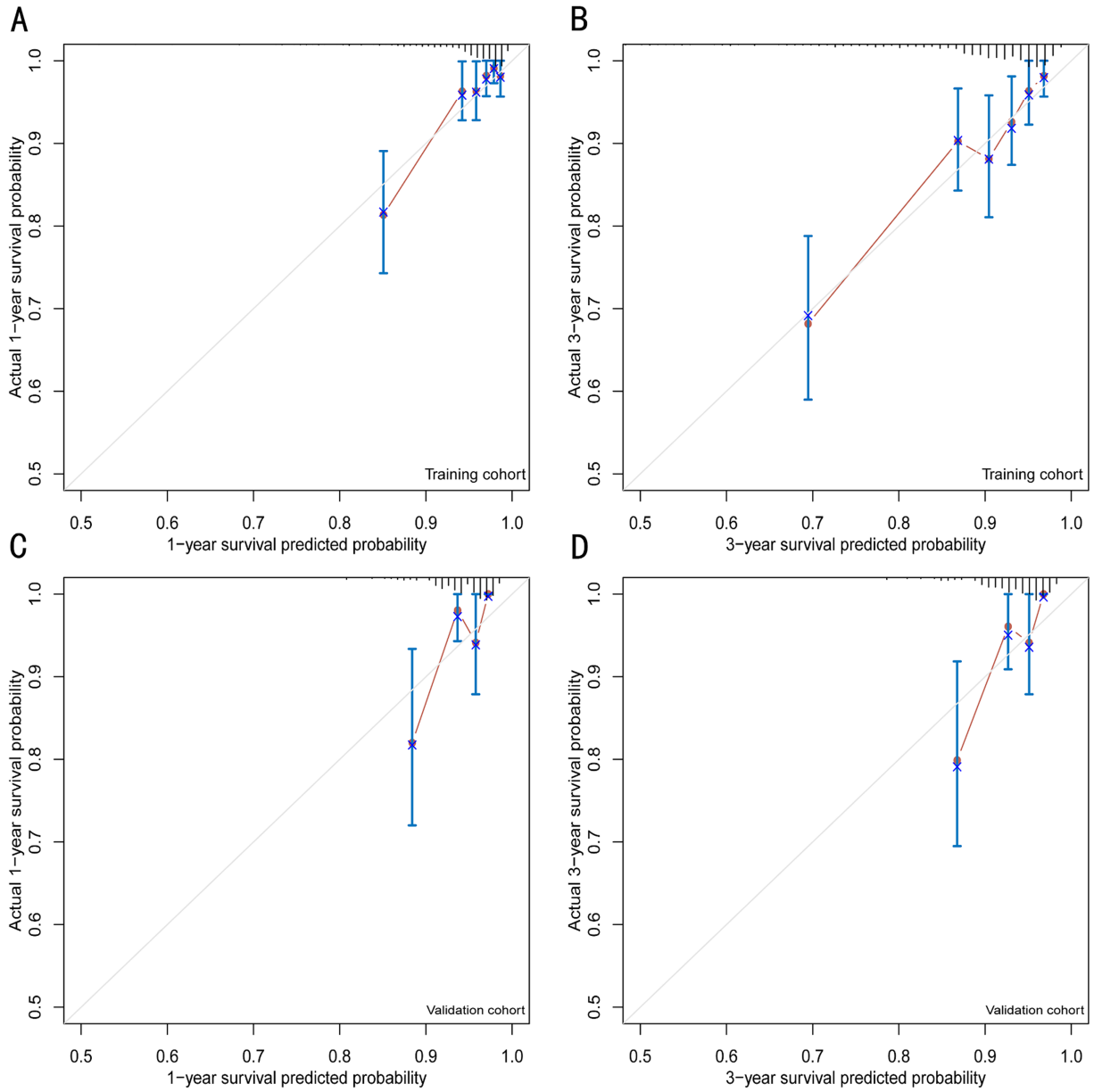

FIGURE 5
Calibration plots for 1- and 3-year survival prediction of the VIP score model. **(A)** Calibration plots for internal validation of the 1-year survival prediction using the training cohort. **(B)** Calibration plots for internal validation of the 3-year survival prediction using the training cohort. **(C)** Calibration plots for external validation of the 1-year survival prediction using the validation cohort. **(D)** Calibration plots for external validation of the 3-year survival prediction using the validation cohort.

TABLE 2 The C-index of the VIP score model compared to the Child–Pugh, MELD, ALBI, FIPS, and CCG-AVB-TEP1 score models.

Model	Training cohort, C-index [95% CI]	*p*	Validation cohort, C-index [95% CI]	*p*
VIPs	0.733 [0.665–0.788]	–	0.869 [0.795–0.918]	–
Child–Pugh	0.672 [0.603–0.740]	<0.001	0.718 [0.640–0.796]	<0.001
MELD	0.601 [0.534–0.664]	<0.001	0.564 [0.439–0.689]	<0.001
ALBI	0.658 [0.593–0.723]	<0.001	0.641 [0.523–0.759]	<0.001
FIPS	0.652 [0.584–0.724]	<0.001	0.632 [0.522–0.742]	<0.001
CCG-AVB-TEP1	0.701 [0.640–0.765]	<0.001	0.690 [0.586–0.794]	<0.001

VIPs, Viral-associated Index of Post-TIPS score; CI, confidence interval; MELD, Model for End-Stage Liver Disease; ALBI, albumin–bilirubin; FIPS, Freiburg index of post-TIPS survival; CCG-AVB-TEP1, Chinese Collaboration Group on the Acute Variceal Bleeding score and Predicting the Treatment Effect.

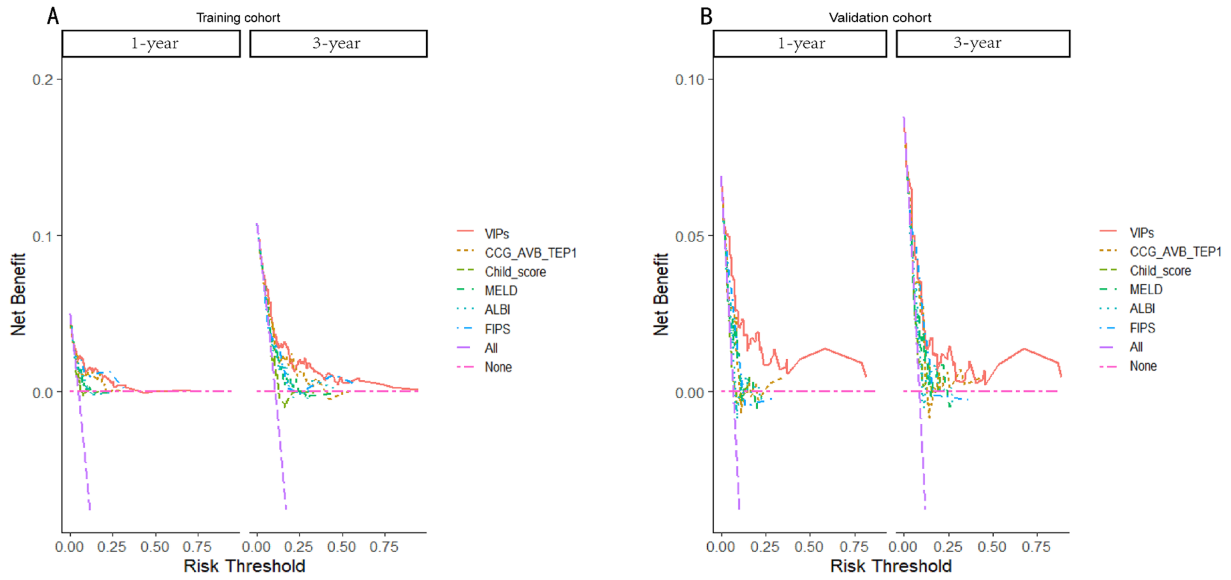

FIGURE 6
Decision curves of the VIP score model and other score prediction models for 1- and 3-year survival prediction after TIPS. **(A)** Decision curves for 1- and 3-year survival prediction using the training cohort. **(B)** Decision curves for 1- and 3-year survival prediction using the validation cohort.

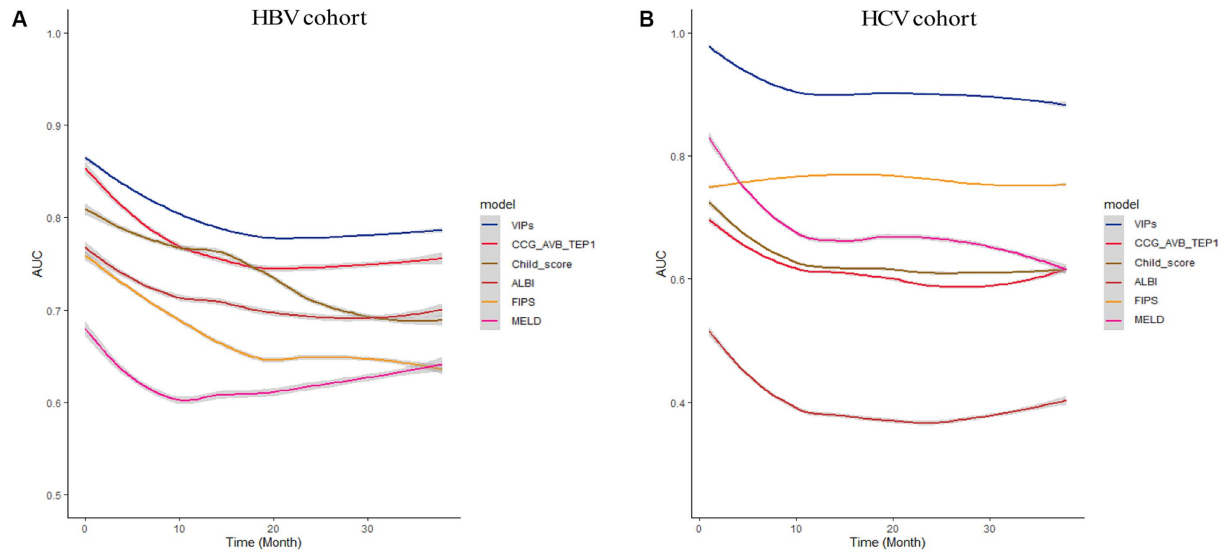

FIGURE 7
Subgroup analysis of HBV cohort and HCV cohort. The time-dependent area under the ROC curve (AUC) of the VIP score compared with other existing scores for 1- and 3-year survival prediction in the HBV cohort **(A)** and HCV cohort **(B)**.

patients had severe renal impairment in our study. In fact, creatinine is the most controversial scoring parameter because it has many influencing factors in patients with liver cirrhosis, such as age, sex, malnutrition, sarcopenia, and drugs. Furthermore, patients with non-liver-related renal dysfunction cannot be effectively identified. However, several studies have shown that renal function improves significantly after TIPS in patients with preoperative renal insufficiency. Hence, our study showed that creatinine is not an independent prognostic factor in patients undergoing TIPS implantation.

This study has several limitations. First, our exclusion criteria included patients with preoperative hepatocellular carcinoma, so our score is not applicable to these populations. Second, the sample size was calculated based on the univariate screening results, rather than all variables, which may overestimate the power. Third, preoperative parameters such as serum albumin, serum sodium level, and ascites volume are easily affected by treatment factors. However, insufficient data on patients' preoperative treatment strategies make it challenging to calibrate the baseline parameters, which may affect the predictive performance of our model. Fourth, the result may not be generalized

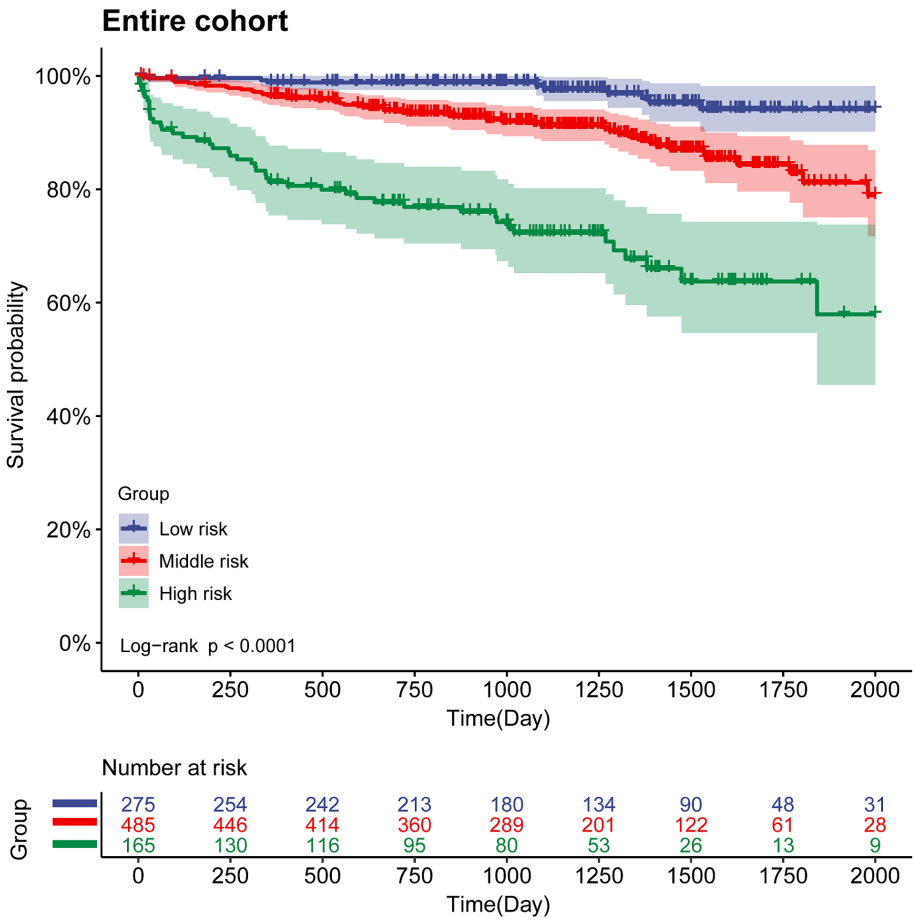

FIGURE 8
Overall survival risk stratification of the VIP score model in the entire cohort.

to other populations/ethnicities. Finally, our external validation cohort was relatively small. Additional sample sizes for validation are needed.

5 Conclusion

We developed and externally validated a prognostic score for TIPS placement based on the largest cohort of patients with viral hepatitis cirrhosis-related portal hypertension using variables that are easily accessible in clinical practice. This risk score can stratify patients into low-, medium-, and high-risk groups and predict their 1-year and 3-year survival rates after TIPS placement. This information helps patients and their families make informed decisions and enables doctors to develop personalized treatment strategies. Although our score performed well overall, it still needs to be validated in larger cohorts or higher-quality studies, which should be the focus of future studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Army Medical Center of PLA. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZQ: Formal analysis, Visualization, Writing – original draft. MW: Formal analysis, Visualization, Writing – original draft. SL: Formal analysis, Visualization, Writing – original draft. LeW: Formal analysis, Visualization, Writing – original draft. ZM: Data curation, Writing – original draft. JY: Data curation, Writing – original draft. WX: Data curation, Writing – original draft. HH: Data curation, Writing – original draft. AL: Data curation, Writing – original draft. XA: Data curation, Writing – original draft. HY: Data curation, Writing – original draft. QC: Data curation, Writing – original draft. YZ: Data curation, Writing – original draft. WL: Data curation,

Writing – original draft. JW: Supervision, Writing – review & editing. DC: Supervision, Writing – review & editing. FL: Conceptualization, Writing – review & editing. DZ: Methodology, Writing – review & editing. LiW: Conceptualization, Funding acquisition, Methodology, Writing – review & editing.

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Conflict of 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.

Publisher's note

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Liver transplantation and comprehensive rehabilitation in the reversal of hepatic myelopathy: a case report

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Hepatic myelopathy (HM) is a rare complication of end-stage chronic liver disease, primarily presenting as symmetrical lower limb weakness that progresses to spastic paralysis without sensory or sphincter dysfunction. We report a case of decompensated cirrhosis associated with hepatitis B virus and HM. The patient showed significant recovery after liver transplantation (LT) and comprehensive rehabilitation training. We summarize the patient's clinical characteristics post-diagnosis and the assessment outcomes following integrated treatment.

KEYWORDS

hepatic myelopathy, spastic paraplegia, portosystemic shunt, liver transplantation, rehabilitation

1 Introduction

Hepatic myelopathy (HM) was first reported in 1949 (1). It is a rare complication of the central nervous system associated with the terminal stage of chronic liver disease, primarily caused by alcoholic cirrhosis and hepatitis B cirrhosis. The occurrence of HM following acute fulminant hepatic failure is infrequent (2). In most documented cases, HM presents as spastic paraplegia of the lower limbs, with rare instances of tetraplegia. Physical examination typically reveals increased muscle tone and hyperreflexia in the lower limbs, without sensory or sphincter dysfunction (3). Research indicates that males, and patients who have undergone splenectomy, splenorenal shunting, or transjugular intrahepatic portosystemic shunt (TIPS), especially those with recurrent episodes of hepatic encephalopathy, are at higher risk for developing HM (4). The onset of HM is often insidious, and the diagnosis is primarily exclusionary, necessitating the elimination of various structural and primary neurological disorders in the context of a highly suspicious clinical presentation. Conservative treatment with ammonia-lowering agents and other medications has shown limited effectiveness, emphasizing the importance of liver transplantation for early-stage patients (5, 6). Here, we present a case of an adult male who developed lower limb weakness 5 months post-TIPS placement and showed a favorable recovery following liver transplantation (LT) and comprehensive rehabilitation training.

2 Case presentation

The patient was a 35-year-old Chinese (Asian) male who initially presented on February 1, 2016, with a 1-week history of abdominal distension. He was diagnosed with hepatitis B

cirrhosis after testing positive for HBsAg. On March 1, 2016, the patient presented with complaints of fatigue and gum bleeding. Upon admission, laboratory investigations revealed a white blood cell count of 2.14×10^9/L (reference range: $4.0–10.0 \times 10^9$/L), a hemoglobin concentration of 124 g/L (reference range: 120–160 g/L), and a platelet count of 37×10^9/L (reference range: $100–300 \times 10^9$/L). Gastrointestinal endoscopy identified multiple esophageal varices situated 25 cm from the incisors, in addition to a tumor-like varix in the gastric fundus. Ultrasonographic evaluation demonstrated splenomegaly, with a longitudinal diameter of 177 mm, splenic hilum thickness of 63 mm, and a splenic vein diameter of 16 mm. On the sixth day of hospitalization, the patient underwent splenectomy and esophagogastric devascularization under general anesthesia. Following discharge, he was prescribed antiviral therapy and hepatoprotective medications. Despite these treatments, the patient experienced recurrent complications, including persistent episodes of diarrhea, gum bleeding, epistaxis, pulmonary infections, and pleural effusions. On May 9, 2023, the patient was admitted to the emergency department due to hematemesis-induced coma. Upon admission, vital signs indicated severe hypotension with a blood pressure of 76/39 mmHg, and laboratory tests revealed critically low hemoglobin levels of 47 g/L. Abdominal computed tomography (CT) imaging suggested cirrhosis, characterized by a linear hyperdense signal between the liver and stomach. The clinical diagnosis was esophagogastric variceal hemorrhage secondary to cirrhosis. The patient underwent urgent interventions, including transjugular gastric variceal embolization and TIPS placement. During hospitalization in June 2023, he exhibited recurrent cognitive decline, leading to a diagnosis of hepatic encephalopathy. The patient also showed signs of poor mental status, with multiple episodes of prothrombin activity below 40%, indicating liver failure. On October 5, 2023, he developed stiffness while walking, which progressively worsened without significant sensory impairment in the lower limbs. By November 2023, these symptoms worsened, accompanied by pitting edema in the lower limbs. He was subsequently admitted to the hepatobiliary surgery department of a hospital in Beijing, where he was diagnosed with HM. Upon admission, his blood ammonia level was 132.5 μmol/L (normal range: 10–47 μmol/L). Neurological examination revealed spastic paraplegia in the lower limbs with muscle strength at grade 2, increased muscle tone, and an inability to stand independently; upper limb function was normal. On December 1, 2023, after completing relevant examinations, the patient underwent LT from a brain-dead donor. One month postoperatively, the patient still exhibited difficulty lifting his legs from the bed, but the rigidity had decreased. The progression of the patient's condition since the diagnosis of cirrhosis is illustrated in Figure 1.

On February 3, 2024, the patient presented to our department of movement rehabilitation with difficulty walking, decreased muscle strength in the lower limbs, and abnormally increased muscle tone. Upon admission, a neurological examination revealed spastic paraplegia, with the ability to walk with 90% weight-bearing status using a scissoring gait. The muscle strength in the lower limbs was grade 3, accompanied by hyperactive deep tendon reflexes and positive bilateral Babinski signs. There were no superficial or deep sensory disturbances, nor symptoms of intestinal or bladder involvement. Cranial nerve examination was normal. The patient's liver function and total bilirubin levels were within the normal range, with detailed hematological and biochemical characteristics shown in Table 1. Brain MRI showed lesions in the frontal lobe and bilateral basal ganglia, suggesting degeneration (Figures 2A,B). MRI of the cervical and lumbar spine showed no significant abnormalities, but MRI of the thoracic spine (T2–T8) revealed thickening and tortuosity of the capillary plexus within the dural sac, with poor flow void effect in some vessels (Figures 2C–E). Motor evoked potentials showed no significant abnormalities, while somatosensory evoked potentials indicated delayed deep sensory conduction in the lower limbs, with no other abnormalities. In terms of treatment, the patient received comprehensive

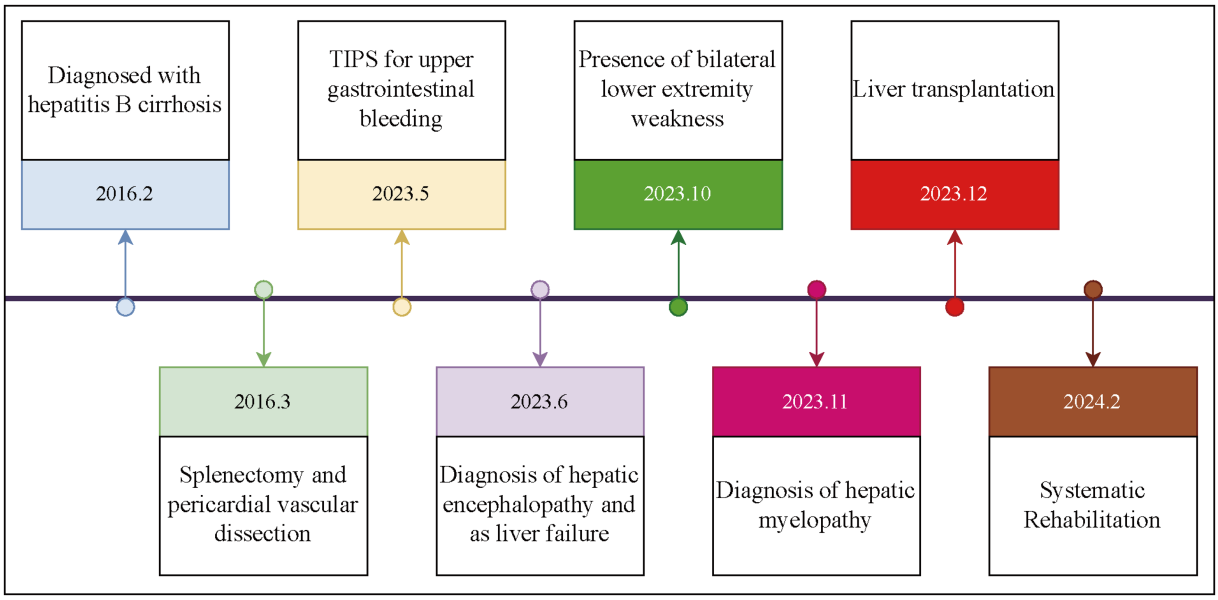

FIGURE 1
Course of the patient from the diagnosis of liver cirrhosis to the initiation of treatment.

TABLE 1 Hematological, biochemical, and nutritional characteristics of the patient at key time points.

Test item (Unit)	Splenectomy	TIPS	LT	Rehabilitation	Reference range
H/W (cm/kg)	184/NA	184/70	184/74	184/69	NA
BMI (kg/m^2)	NA	20.7	21.9	20.4	18.5–23.9
ALT (U/L)	31.1	30.1	25.4	13.0	9–50
AST (U/L)	24.9	39.7	52.1	18.3	15–40
ALP (g/L)	NA	64.7	94.1	40.5	40–55
GGT (U/L)	NA	24.5	26.0	15.5	0–125
CHE (U/L)	NA	1,689	1944	10,050	5,320–12,920
TBIL (μmol/L)	32.1	45.8	73.9	7.3	17–23
DBIL (μmol/L)	19.2	21.1	45.7	3.8	0–8
TBA (μmol/L)	NA	14.6	230.0	7.2	0–10
TP (g/L)	61.4	49.0	55.9	60.8	65–85
ALB (g/L)	36.3	20.8	29.5	45.2	35–52
GLB (g/L)	25.1	28.2	26.5	31.6	20–35
PREA (mg/dL)	NA	NA	0.04	0.31	0.2–0.34
TRIG (mmol/L)	0.7	1.0	0.7	0.9	0–1.7
CHOL (mmol/L)	3.1	3.3	3.1	4.1	0–5.2
HDL-C	1.60	1.40	1.12	1.78	0.77–2.25
LDL-C	1.07	1.30	1.54	2.35	0–3.36
Apo-A1 (mg/dL)	NA	0.77	1.10	1.43	1.2–1.6
Apo-B (mg/dL)	NA	0.55	0.51	0.89	0.8–1.1
sd LDL-C (mmol/L)	NA	0.11	0.14	0.66	0.246–1.393
PT (s)	11.5	17.7	12.1	12.6	10–13
APTT (s)	23.1	65.4	25.5	26.1	23.3–32.5
FIB (g/L)	2.9	1.05	3.62	1.91	1.8–3.5
Mn (μmol/L)	NA	NA	NA	Normal	0–255
Vitamin B1 (ng/mL)	NA	NA	Normal	Normal	80–200
Vitamin B6 (nmol/L)	NA	NA	Normal	Normal	20–200
Vitamin B12 (pmol/L)	NA	NA	Normal	Normal	133–675
25-HD (nmol/L)	NA	Normal	Normal	16	25–150

H/W, Height/Weight; BMI, Body mass index; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma-glutamyl transferase; CHE, Cholinesterase; TBIL, Total bilirubin; DBIL, Direct bilirubin; TBA, Total bile acid; TP, Total protein; ALB, Albumin; GLB, Globulin; PREA, Prealbumin; TRIG, Triglycerides; CHOL, Cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; Apo-A1, Apolipoprotein AI; Apo-B, Apolipoprotein B; sd LDL-C, Small dense low-density lipoprotein cholesterol; PT, Prothrombin time; APTT, Activated partial thromboplastin time; FIB, Fibrinogen; Mn, Manganese; Vitamin B1, Thiamine; Vitamin B6, Pyridoxine; Vitamin B12, Cobalamin; 25-HD, 25-Hydroxyvitamin D; NA, Not available; s, second.

rehabilitation training while maintaining anti-rejection and antiviral therapies. This included physical therapy (PT) for paraplegic patients, psychological counseling, social and vocational rehabilitation, respiratory training, neuromuscular electrical stimulation, peripheral repetitive magnetic stimulation, aquatic exercises, and acupuncture treatment. The patient was discharged after 40 days and continued with weekly remote rehabilitation guidance training. Assessments using relevant scales were conducted before and after rehabilitation treatment, and at the first and third months of follow-up. These included the Spinal Cord Injury Motor Score (SCIM), Functional Independence Measure (FIM), Walking Index for Spinal Cord Injury (WISCI), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), and the Impact of Event Scale-Revised (IES-R). The assessment results are shown in Figure 3. 6 month post-transplantation, the patient's liver function and total bilirubin levels remained normal. The muscle strength in the lower limbs improved to grade 4, allowing for independent walking of approximately 50 m, with an improved scissoring gait compared to before. No other neurological symptoms were reported during the follow-up period.

3 Discussion

Hepatic myelopathy is a relatively rare neurologic complication associated with advanced liver disease, often underdiagnosed due to its low incidence in clinical practice. It is commonly believed to be related to the spontaneous formation of portal-systemic shunts or

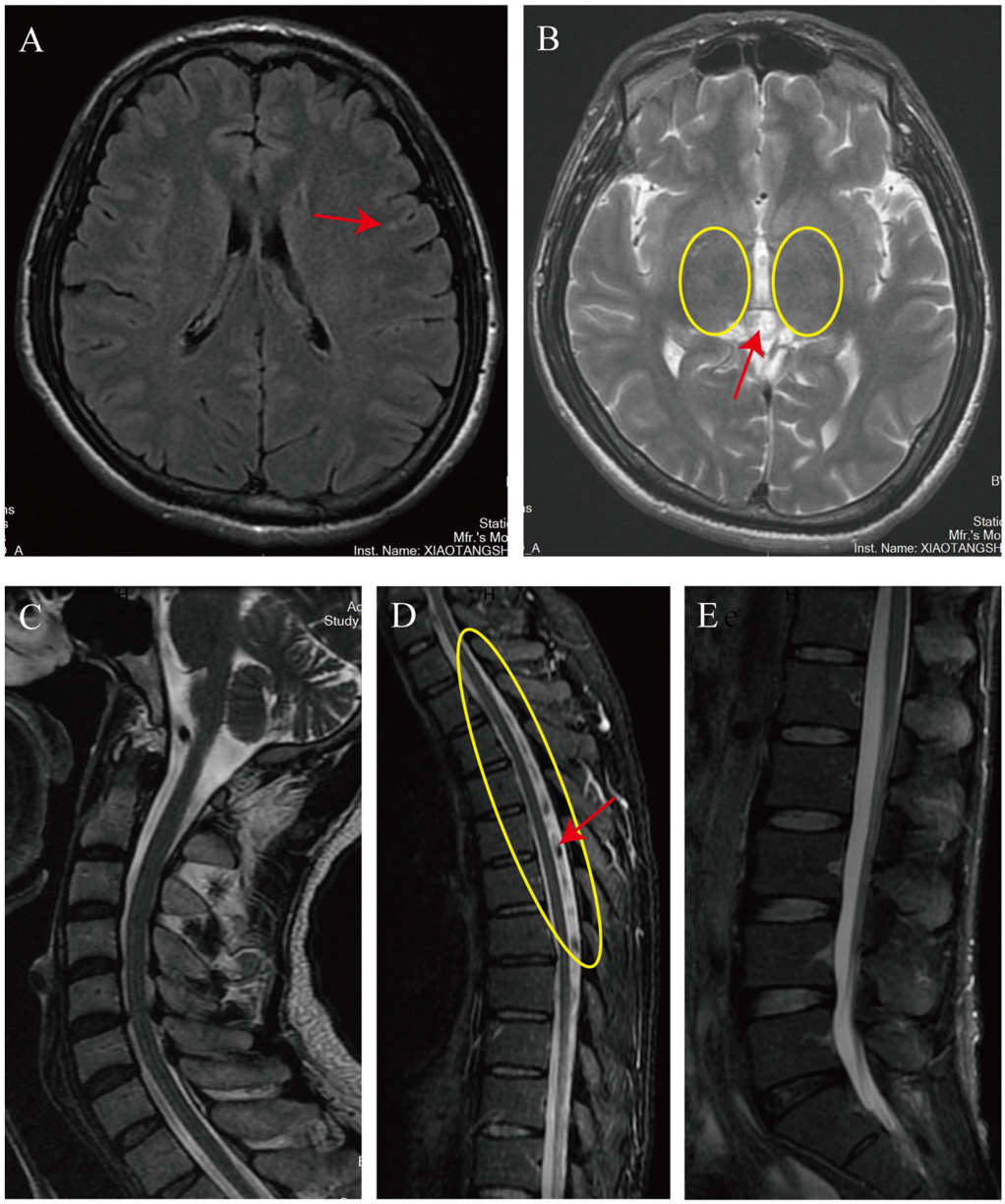

FIGURE 2
The imaging findings upon the patient's admission. The cranial MRI reveals patchy T2-FLAIR hyperintense signals in the left frontal lobe (indicated by the red arrow in **A**). Additionally, it shows faintly hyperintense, slightly increased signals in the bilateral basal ganglia on T2-weighted images (encircled in yellow in **B**) and an isointense pineal gland with a diameter of approximately 11 mm (also indicated by the red arrow in **A**). The MRI of the entire cervical and lumbar spinal cord shows no significant abnormalities **(C,E)**. However, the thoracic spine MRI demonstrates a tortuous and thickened capillary plexus within the dural sac on T2-weighted images from T2 to T8 (encircled in yellow in **D**), with some vessels exhibiting a poor flow void effect (indicated by the red arrow in **D**).

surgeries performed on patients with liver disease. The characteristic features of HM include bilateral, chronic, progressive, symmetric spastic paraplegia, with rare involvement of the sphincters and sensory systems, and severe myopathy accompanied by extensive portal collateral circulation (7, 8). In this case, the patient developed HM 5 months after the TIPS procedure, exhibiting clinical symptoms similar to those previously reported.

The exact pathogenesis of HM is not fully understood due to the lack of a mature animal model to simulate the disease process. Current research suggests that the onset of HM may involve multiple pathophysiological mechanisms, including toxic damage, nutritional deficiency, hemodynamic changes, and immune damage (9). The toxic damage mechanism posits that ammonia and other nitrogenous toxins accumulate when liver function is impaired, crossing the blood–brain barrier and causing neuronal damage, potentially leading to symmetrical demyelination of the corticospinal tracts, which is one of the early spinal cord injury characteristics of HM (10). In this case, the patient had multiple episodes of elevated blood ammonia levels before LT, likely contributing to the progression of HM. The lesions may also involve the giant Betz cells in the internal layer of the precentral gyrus of the cerebral cortex, which are the nutritional centers of the corticospinal tracts. This can lead to gradual

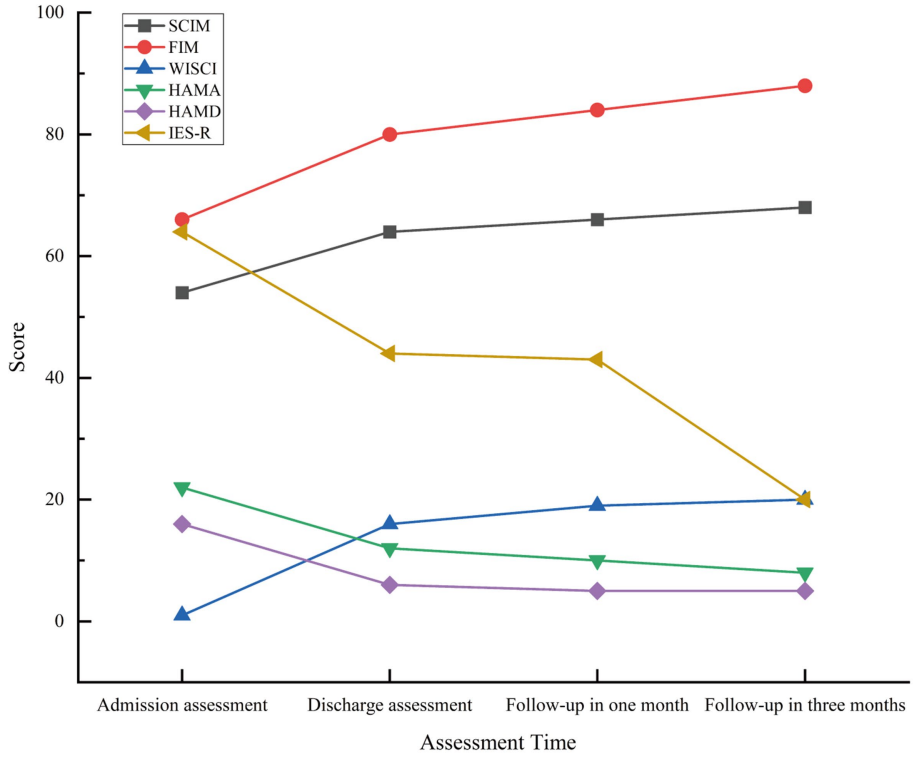

FIGURE 3
Patient scale assessment results, including admission and follow-up evaluations.

degeneration and loss of nerve fibers from the distal to the proximal end, with severe cases extending to the brainstem and internal capsules, ultimately causing irreversible spinal cord nerve tissue damage. The nutritional deficiency mechanism emphasizes the impact of liver insufficiency on the absorption and synthesis of neuroprotective substances. Deficiencies in vitamins, phospholipids, and other substances may lead to a lack of proteins and enzymes in spinal cord nerve fiber cells, thereby affecting the synthesis and renewal of neurotransmitters (11). In this case, the blood ammonia, manganese ions, and vitamin levels checked after admission were within the normal range, likely due to the recovery of liver function after liver transplantation. However, due to the lack of these indicators before liver transplantation, it is not possible to exclude whether these factors impacted the progression of the patient's HM. The hemodynamic change mechanism focuses on the potential impact of portal hypertension and its spontaneous shunting phenomenon on the onset of HM. Long-term portal hypertension may lead to chronic ischemia and hypoxia of the thoracolumbar spinal cord, especially in areas with obvious segmental characteristics of blood supply, such as the abdominal lateral wall of the fourth thoracic and first lumbar segments, where spinal cord damage is particularly obvious (12). In this case, the thoracic spine MRI at the T2–T8 segment showed tortuous and thickened capillary plexus within the dural sac, with poor flow void effect in some vessels, indicating poor blood flow in this segment of the spinal cord. This is likely to lead to chronic ischemia and hypoxia of this segment of the spinal cord, resulting in corresponding clinical symptoms. The immune damage mechanism suggests that chronic liver disease, mainly caused by viral infections, may cause spinal cord nerve damage through the deposition of immune complexes in the nervous system. In summary, the pathogenesis of HM is the result of multiple factors and mechanisms acting together. Future research needs to further explore the interaction between these mechanisms and how they jointly affect the pathological process of HM. Additionally, the development of effective animal models is crucial for a deeper understanding of the pathogenesis of HM and for finding potential treatment methods.

The diagnosis of HM requires the exclusion of other causes of spastic paraplegia, such as subacute combined degeneration of the spinal cord caused by vitamin B12 deficiency, hepatolenticular degeneration, primary lateral sclerosis, multiple sclerosis, and hereditary spastic paraplegia. Laboratory biochemical test results usually relate to liver dysfunction or cirrhosis, such as increased blood ammonia levels, abnormal liver function indicators, and abnormal coagulation function (13). Cranial MRI in patients with HM may show high signals in the basal ganglia on T1-weighted imaging (14). In this case, abnormal signals in the frontal lobe and bilateral basal ganglia may be related to the aforementioned pathogenesis, but it cannot be excluded that they are related to the patient's history of syncope and ischemia of the cortex and deep nuclei caused by hepatic encephalopathy. In most cases, head imaging examinations of patients with HM do not show obvious abnormalities. In terms of electrophysiology, Nardone et al. showed that the central motor conduction time (CMCT) of patients with HM was prolonged, which is a key indicator of the conduction time from motor cortical neurons to spinal motor neurons. Its prolongation reflects damage to the corticospinal tract, the main nerve fiber bundle controlling voluntary movement of skeletal muscles. This damage may be the main reason for the motor disorders of patients with HM. The study

also pointed out that before the patient develops sensory disorders, the damage to the sensory pathway can be assessed by electrophysiological assessment of central sensory conduction (15). These findings emphasize the importance of electrophysiological testing in the early diagnosis of HM, especially in the preclinical stage. A significant increase in CMCT may indicate a reduction in the recovery of HM nerve function. In this case, there was a lack of corresponding electrophysiological testing in the early stage, and the relevant electrophysiological testing after admission showed no obvious abnormalities in CMCT, which may provide the possibility for the patient's further recovery. Although the patient's physical examination showed no obvious sensory abnormalities, the somatosensory evoked potential test showed delayed conduction in the deep sensory conduction pathway of the lower limbs, which may also be an important factor affecting the patient's balance function.

At present, there is no proven effective treatment for HM. Existing literature indicates that LT can significantly alleviate the clinical symptoms of patients with HM and may be effective (5, 6, 16), but the effect of LT on patients with advanced HM is not obvious (17). Timely control of blood ammonia may prevent the further development of HM and improve the patient's prognosis (7). There are reports that embolization of some parts of the splenic artery can alleviate severe spastic HM, thereby greatly reversing the severe spastic paraplegia caused by HM (18). Sun et al. were the first to apply fecal microbiota transplantation to treat HM (19). In this case, the patient underwent systematic rehabilitation training after LT, including a long-term plan for subsequent remote rehabilitation, while emphasizing the repair of psychological trauma during the rehabilitation process. This included the use of cognitive therapy, spiritual reshaping therapy, and music therapy. In comprehensive rehabilitation training, the patient achieved good benefits in both psychological and life ability aspects, providing some reference for future cases.

4 Conclusion

In summary, HM typically presents clinically as a chronic, progressive spastic paraplegia of the lower limbs. However, the underlying pathophysiology remains elusive. Specific biochemical markers, electrophysiological assessments of central sensory-motor conduction, and thoracic spinal MRI hold significant potential for aiding in the diagnosis and prognostication of HM. LT combined with comprehensive rehabilitation protocols has been proposed as a potentially effective therapeutic approach. Nevertheless, current literature on this condition is sparse, and standardized rehabilitation protocols for HM are lacking, underscoring the need for further prospective studies to validate these findings. Moreover, innovative treatment modalities, such as advanced surgical techniques and fecal microbiota transplantation, warrant further investigation.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Beijing Xiaotangshan Hospital Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ML: Formal analysis, Resources, Visualization, Writing – original draft, Writing – review & editing. RW: Resources, Writing – review & editing. WZ: Resources, Writing – review & editing. CT: Resources, Writing – review & editing. QW: Resources, Writing – review & editing. QZ: Resources, Writing – review & editing. SJ: Supervision, Writing – review & editing. LW: Resources, Supervision, Writing – review & editing.

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Conflict of 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.

Publisher's note

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Correlation between the diameter of esophageal varices measured using a virtual ruler under endoscopy and portal pressure gradient

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Background: Esophageal variceal diameter (EVD) is a crucial factor in determining the risk of esophageal variceal bleeding, which is associated with an increased portal pressure gradient (PPG). However, research into the relationship between EVD and PPG has been limited, primarily because the assessment of EVD depends on visual estimation during endoscopy. Recently, we developed an artificial intelligence (AI)-based method to accurately detect EVD. In this study, we aim to investigate the correlation between EVD and PPG, with the goal of evaluating EVD as a potential non-invasive indicator of PPG.

Methods: This study included both retrospective and prospective data from 128 patients diagnosed with portal hypertension and gastroesophageal varices, gathered from two medical institutions. Clinical data including PPG, biochemical markers, and routine blood tests were collected. In the retrospective phase, EVD was evaluated using an AI-based virtual ruler. In the prospective phase, PPG was measured using radiological intervention methods, and EVD was measured during endoscopy with the aid of AI.

Results: A positive correlation between PPG and EVD was identified ($r = 0.521$, $P < 0.001$), which was further supported by multivariate linear regression analysis (b = 6.521, t = 6.872, $P < 0.001$). When patients were stratified into two groups based on PPG levels (27 patients with PPG $<$ 20 mmHg and 101 patients with PPG $\geq$ 20 mmHg), a significant difference in EVD was observed between the groups (OR = 29.275, 95% CI 5.590–153.304, $P < 0.001$), with larger EVD in the higher PPG group. These findings suggest that EVD may serve as a predictor of adverse events associated with elevated PPG levels. In addition, receiver operating characteristic (ROC) curve analysis showed that EVD had an accuracy of 0.814 in diagnosing PPG function (standard error 0.048, 95% CI 0.720-0.908; P $<$ 0.001), indicating that PPG levels are likely to exceed 20 mmHg when the variceal diameter is greater than 1.1 cm.

Conclusion: EVD demonstrated a positive correlation with PPG and could potentially be used as a predictive marker for assessing PPG levels. These findings provide novel insights for the non-invasive evaluation of PPG in clinical practice.

KEYWORDS

portal pressure gradient, esophageal vein diameter, liver cirrhosis, esophageal varices, portal hypertension

Introduction

Portal hypertension (PH), a major pathological consequence of cirrhosis, leads to various clinical manifestations and severe complications, including ascites, varices, variceal bleeding, hepatic encephalopathy, and even cardiac and pulmonary complications. Bleeding from gastroesophageal varices is a common and life-threatening complication of liver cirrhosis, with the highest and most concerning mortality rates reported (1, 2). Due to the poor prognosis associated with variceal bleeding, previous studies and clinical guidelines have focused on identifying predictors and implementing preventive interventions for patients at high risk of bleeding. The primary goal of screening and monitoring is to identify individuals at high risk of esophageal variceal bleeding (EVB), thereby facilitating the timely implementation of prevention strategies.

Portal pressure gradient (PPG) and hepatic venous pressure gradient (HVPG) are recognized as the gold standard for diagnosing PH. The levels of PPG or HVPG are closely associated with the development of varices, variceal bleeding (3, 4), shunt dysfunction, and patient survival (5). However, measuring PPG or HVPG is invasive, time-consuming, and costly, making it impractical for routine clinical use. Patients may also be reluctant to undergo these tests solely for examination purposes. Therefore, the search for non-invasive tools to predict the development or bleeding of esophageal varices (EV) has garnered significant interest among clinical professionals. Researchers have discovered that non-invasive methods are increasingly preferred over PPG or HVPG in clinical practice. For instance, evidence has shown that the severity of varices with red wale marks is linked to an increased risk of bleeding (6), and liver stiffness combined with the spleen/platelet ratio is associated with varices requiring treatment (7).

It is well established that esophageal variceal pressure rises with increasing portal vein pressure (PVP). According to Laplace's law, the tension in the blood vessel wall is positively correlated with the square of the radius (r^2), making vessel diameter a critical factor among several influencing variables. An increase in diameter results in thinning of the blood vessel wall and the appearance of red wale marks. When the tension exceeds a certain threshold, the vessel wall ruptures, resulting in bleeding. While current evidence suggests that an increase in esophageal variceal diameter (EVD) can predict the risk of bleeding, the correlation between EVD and HVPG or PPG has not yet been established. If the bleeding risk threshold of HVPG or PPG could be accurately predicted through EVD, it would significantly facilitate the prediction of bleeding and prognosis using endoscopic examination.

Despite significant updates in the management of gastroesophageal varices in recent years, particularly in the use of non-invasive methods to assess the degree of PH, it is essential to continuously identify factors that predict the risk of EVB and long-term prognosis. According to our previous research, EVD can be determined accurately using a non-invasive technology, called a virtual ruler (VR), supported by artificial intelligence (AI) developed by our team.

We also found that EVD significantly reduced rebleeding rates after endoscopic variceal ligation, and the risk of rebleeding increased notably when EVD exceeded 1.35 cm (8). Our study aimed to evaluate and establish the correlation between PPG and EVD through endoscopic examination. This involved multicenter retrospective and prospective analyses to predict PPG by measuring EVD endoscopically. The goal was to provide clinical evidence for predicting bleeding risk using non-invasive methods.

Materials and methods

Patients

The study encompassed data from both retrospective and prospective research, involving a total of 128 patients with PH and gastroesophageal varices. In the retrospective phase, 64 patients who underwent transjugular intrahepatic portosystemic shunt (TIPS) creation were selected from the First Affiliated Hospital of Anhui Medical University. This part of the study was conducted from July 2019 to January 2022. In the prospective phase, 12 patients who underwent TIPS creation were also selected from the same medical institution from March 2022 to January 2023, while 52 patients who received endoscopic selective varices devascularization were selected from the First Affiliated Hospital of the University of Science and Technology of China (USTC) from February 2022 to August 2023.

The clinical analysis was approved by the ethics committee of the First Affiliated Hospital of Anhui Medical University (NO. PJ20221016) and the Medical Research Ethics Committee of the First Affiliated Hospital of USTC (NO. PJ024E45). The inclusion criteria were as follows: (1) age between 18 and 75 years, (2) confirmation of EV through endoscopy, and (3) normal diameter of the hepatic vein and inferior vena cava. The exclusion criteria were as follows: (1) acute infection status, (2) use of medications affecting PVP in the past week, and (3) presence of portal vein thrombosis.

Clinical data collection

Patients' clinical data were collected from the Electronic Medical Record System or during the general treatment process, including etiology, spleen size, Child-Pugh score, prothrombin time (PT), serum levels of alanine aminotransferase (ALT), total bilirubin (TBiL), albumin (ALB), creatinine (Cr), white blood cell (WBC) count, hemoglobin (HB), platelet (PLT) count, and the presence of ascites. Ascites were categorized into four levels based on the depth of fluid observed via abdominal ultrasound: no ascites (level 0, none), small amounts of ascites (level 1, 0–30 mm), moderate amounts of ascites (level 2, 30–60 mm), and large amounts of ascites (level 3, more than 60 mm). The Child-Pugh grade is represented as a numerical value in statistical analysis: Child-Pugh A as grade 1, Child-Pugh B as grade 2, and Child-Pugh C as grade 3.

Measurement of PPG

For the retrospective data, the information regarding PPG was extracted from the Electronic Medical Record System. In the prospective phase, PPG was measured by attending interventional radiologists with more than 10 years of experience or senior physicians. The procedures were performed after clarifying the patient's diagnosis and clinical condition. For patients undergoing endoscopic selective varices devascularization, the left branch of the portal vein was punctured under ultrasound guidance to inject an appropriate contrast agent for portal vein imaging.

An introducer sheath and microwires were inserted into the portal vein to measure PVP. The right internal jugular vein approach was then used with a balloon catheter to measure wedged hepatic venous pressure (WHVP). After releasing the balloon, free hepatic vein pressure (FHVP) and inferior vena cava pressure (IVCP) were measured. The PPG was calculated using the formula: PPG = PVP − IVCP. Preoperative and postoperative PVP and IVCP were measured using the transjugular approach before performing venous shunt surgery for patients undergoing TIPS. The pressure unit conversion formula is 1 mmHg = 0.735 cmH_2O.

Measurement of EVD

Endoscopic examinations were conducted in all cases, mostly within 1 week before or after the PPG measurements and never exceeding 1 month. A non-invasive technology called VR, supported by AI, was used to measure the diameter of esophageal varices during endoscopy. This technological innovation was developed by our team in a previous study (9). A transparent cap (cat. no. DL-108-40; Micro Tech Co. Ltd.) with an inner diameter of 1 cm was affixed to the tip of the endoscope (cat. no.GIF Q260J; Olympus), and the VR was activated during the endoscopic examination.

The cursor continuously adjusted with the movement of the endoscope, aligning with the transparent cap's discontinuous arc and automatically establishing a coordinate system at the center of the circle (Figure 1). Testing demonstrated that the software package proved to be a valuable and dependable tool for the endoscopic identification and treatment of EV in patients with liver cirrhosis, leading to the acquisition of the National Utility Model Patent (NO. CN115345850A, CN115311239A, CN115345851A). As some patients presented with both small and large EVs, the large varices were selected for analysis. EVD was retrospectively reexamined using a VR or measured during gastroscopy procedures using AI-assisted software, which was jointly operated and averaged by two endoscopists, one of intermediate and the other of senior level, who had undergone the relevant training on the VR technology.

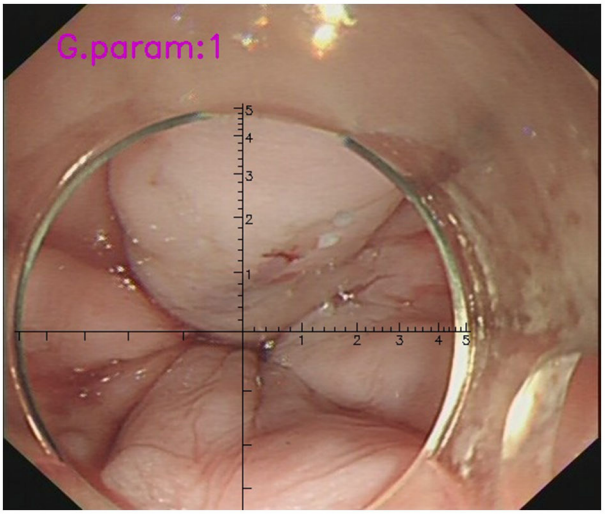

FIGURE 1
The measurement of EVD during gastroscopy with the assistance of VR. AI-assisted software could detect the discontinuous arc of the cap and establish a coordinate system at the center of the circle automatically (the cursor has a scale of 1mm per scale). The diameter of the target EV in the picture was determined to be approximately 0.6 cm.

TABLE 1 Information on all cases.

Cases	Shapiro-Wilk Test	$\chi \pm s$	M (P_{25}, P_{75})
Age (year)	0.200	55.02 ± 11.23	-
PPG (mmHg)	0.223	24.34 ± 4.88	-
SBP (mmHg)	0.200	105.12 ± 9.53	-
DBP (mmHg)	0.058	62.80 ± 7.54	-
EVD (cm)	0.002	-	1.20 (0.80, 1.50)
ALB (g/L)	0.944	31.57 ± 5.96	-
Ascites (grade)	0.000	-	1 (1, 2)
ALT (U/L)	0.000	-	25.00 (17.00, 41.00)
BA (umol/L)	0.005	-	47.75 (25.00, 65.65)
PT (s)	0.016	-	15.20 (13.70, 17.40)
WBC ($\times 10^9$/L)	0.000	-	2.41 (1.56, 3.61)
HB (g/L)	0.033	-	73.00 (63.00, 84.00)
PLT ($\times 10^{12}$/L)	0.000	-	60.00 (38.00, 83.00)
TBiL (umol/L)	0.000	-	20.11 (14.93, 28.98)
Child-Pugh score	0.000	-	8.00 (7.00, 9.88)
Child-Pugh grade	0.000	-	2 (2, 2)

PPG, portal pressure gradient; SBP, systolic blood pressure; DBP, diastolic blood pressure; EVD, the diameter of esophageal varices; ALB, albumin; ALT, alanine aminotransferase; BA, blood ammonia; PT, prothrombin time; WBC, white blood cell; HB, hemoglobin; PLT, platelet; TBiL, total bilirubin.

Statistical analysis

This study utilized Statistical Program for Social Sciences (SPSS) 20.0 software (IBM, SPSS, Inc., Chicago, IL, USA) for statistical analysis. The measurement data followed a normal distribution and were presented as mean ± standard deviation, M ± SD. For non-normal distribution or ordinal

data, the median and interquartile range were used M (P25, P75). An independent samples t-test was used to compare rates and means for normally distributed data, while a non-parametric test was applied for skewed distributions and categorical data. Spearman correlation analysis and binary logistic regression models were utilized to examine the relationship between the diameter of EVD and PPG. The receiver operating characteristic (ROC) curve analysis was performed to assess the accuracy of the esophageal variceal diameter to predict PPG and to determine the cutoff values based on sensitivity and specificity. Statistical significance was determined at a P-value of <0.05.

Results

Case information

The data were collected from a total of 128 patients across two medical institutions, adhering to strict inclusion criteria. This cohort comprised 35 women and 93 men. The primary cause of cirrhosis and PH was hepatitis B virus, accounting for the majority of cases (85, 66.4%), followed by alcoholic cirrhosis (7, 5.5%), autoimmune hepatitis (4, 3.1%), hepatitis C virus (4, 3.1%), and some other causes, such as drug-induced cirrhosis and hepatolenticular degeneration. Additionally, patients with unexplained liver cirrhosis contributed to a significant proportion (23, 18.0%). More detailed patient characteristics are presented in Tables 1, 2.

The correlation between PPG and EVD

The measurement of diameters using the VR showed significant agreement between two endoscopists ($r = 0.994$, $P < 0.001$). The Spearman correlation analysis was performed to evaluate the correlation between EVD and PPG. The results indicated a positive correlation between PPG and EVD (correlation coefficient $r = 0.521$, $P < 0.001$), suggesting that EVD gradually increases with rising PPG. Furthermore, a scatter plot was utilized to illustrate the relationship between the two variables (Figure 2).

To minimize the influence of confounding factors on the research outcomes, variables such as PT, ALT, ALB, TBiL, WBC count, and ascites were incorporated into the construction of a multivariate linear regression model. The results also demonstrated a positive correlation between EVD and PPG ($b = 6.521$, $t = 6.872$, $P < 0.001$).

Predicting PPG through EVD

Previous studies have indicated that as PPG increases, the risk of EVB gradually rises, with PPG $\geq$ 20 mmHg recognized as a criterion for poor prognosis (10). In the current study, clinical data were classified into two groups based on the aforementioned criteria, with 27 cases in the PPG $<$ 20 mmHg group and 101 cases in the PPG $\geq$ 20 mmHg group. T-tests, or non-parametric tests, were employed to analyze the differences between the two groups (Table 3). The results revealed significant variances in EVD ($P < 0.001$), ascites ($P = 0.036$), and white blood cell count ($P = 0.027$).

TABLE 2 Baseline comparison of clinical data from different sources.

Factors	Research type				Medical institution			
	Retrospective ($n = 64$)	Prospective ($n = 64$)	t/Z	P	Institution1 ($n = 52$)	Institution2 ($n = 76$)	t/Z	P
Age	53.16 ± 10.39	56.89 ± 11.81	1.900	0.060	56.98 ± 11.81	53.68 ± 10.69	1.642	0.103
Gender	1 (1, 1)	1 (1, 2)	−1.383	0.167	1 (1, 2)	1 (1, 1.75)	−0.716	0.474
SBP	104.80 ± 9.88	105.44 ± 9.22	0.379	0.705	105.58 ± 9.44	104.80 ± 9.63	0.450	0.653
DBP	62.47 ± 7.21	63.14 ± 7.90	0.502	0.616	63.90 ± 7.91	62.04 ± 7.23	1.392	0.166
EVD	1.20 (0.80, 1.30)	1.20 (0.85, 1.50)	−1.774	0.076	1.20 (0.80, 1.58)	1.20 (0.85, 1.38)	−1.423	0.155
PPG	24.36 ± 4.57	24.32 ± 5.21	−0.046	0.964	23.51 ± 5.18	24.91 ± 4.62	−1.603	0.111
AST	23.00 (17.00, 40.75)	25.50 (19.25, 45.00)	−1.228	0.219	27.00 (21.00, 45.00)	23.00 (16.25, 45.75)	−1.452	0.147
BA	43.50 (17.75, 63.25)	52.25 (36.25, 92.50)	−1.201	0.230	47.70 (35.98, 68.25)	49.00 (18.00, 67.00)	−0.214	0.830
PT	16.2 (14.10, 18.50)	14.65 (13.40, 16.28)	−2.780	0.005	14.65 (13.33, 16.10)	16.00 (13.90, 18.30)	−2.581	0.001
WBC	2.31 (1.66, 3.33)	2.44 (1.51, 3.49)	−0.593	0.553	2.51 (1.12, 3.43)	2.28 (1.53, 3.71)	−0.338	0.735
PLT	65.00 (37.75, 89.00)	55.50 (39.00, 81.25)	−0.798	0.425	60.50 (44.25, 83.00)	58.50 (34.00, 84.00)	−0.756	0.450
TBiL	20.58 (13.03, 30.90)	19.55 (15.75, 27.10)	−0.312	0.755	19.40 (15.03, 27.10)	20.58 (13.12, 30.90)	−0010	0.992
ALB	30.33 ± 5.64	32.81 ± 6.06	2.396	0.018	32.46 ± 5.87	30.97 ± 5.99	1.392	0.161
Ascites	2 (1, 3)	1 (1, 2)	−2.143	0.032	2 (1, 3)	1 (1, 2)	−2.217	0.027
HB	68.50 (62.50, 84.00)	75.00 (62.00, 85.25)	−1.575	0.115	75.00 (63.00, 90.75)	71.00 (61.00, 84.00)	−1.101	0.271
Child–Pugh score	8.00 (7, 10)	8.25 (7, 9)	−0.771	0.441	9.00 (7.00, 9.88)	8.00 (7.00, 9.75)	−0.061	0.951
Child–Pugh grade	2 (2, 3)	2 (2, 2)	−1.378	0.168	2 (2, 2.75)	2 (2, 2)	−0.223	0.823

In our study, a binary logistic regression model was utilized to control for confounding factors on the outcomes. With PPG as the dependent variable, EVD, ALB, ascites, ALT, blood ammonia, PT, WBC, PLT, and TBiL were included to formulate a multivariate logistic regression equation. The results showed that EVD had a statistically significant difference between the two groups (OR = 29.275, 95% CI 5.590–153.304, P < 0.001), with a wider EVD observed in the higher PPG group. These results suggest that EVD can predict adverse events linked to elevated PPG levels, with the risk of bleeding increasing 3.377 times for every 1 mm increase in EVD. Detailed logistic regression analysis results are outlined in Table 4.

The ROC curve analysis (with EVD as the test variable and PPG exceeding 20 mmHg as the state variable) demonstrated that EVD had an accuracy of 0.814 in diagnosing PPG function (standard error 0.048, 95% CI 0.720–0.908; $P < 0.001$) (Figure 3). An EVD cutoff value of 1.1 cm provided 68.3% sensitivity and 81.5% specificity in diagnosing PPG ≥ 20 mmHg, suggesting that PPG levels might exceed 20 mmHg when EVD exceeded 1.1 cm.

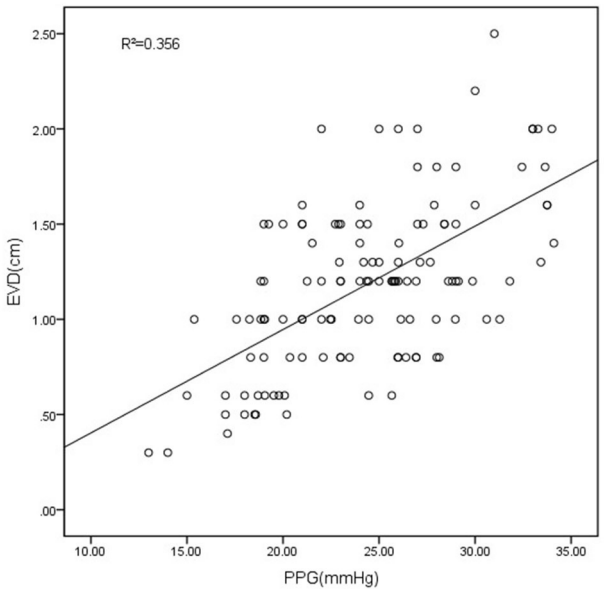

FIGURE 2
The scatter plot showed the correlation between PPG and EVD. EVD measured with VR had a good correlation with the PPG ($R^2 = 0.356$, $P < 0.001$).

Discussion

EVB is a common complication of liver cirrhosis and is closely related to the mortality and morbidity of these patients. The reported mortality rate from acute bleeding episodes accounts for ∼15%−20% of patients with cirrhosis (11). Additionally, the endoscopic grade of EV closely correlates with EVB (12). A recent literature review found few reports on the relationship between PPG and EVD based on endoscopic findings. Therefore, in the present study, the correlation between PPG and EVD was determined through multivariate analysis.

PPG or HVPG plays an important role in the recognized standards for disease assessment and prognosis evaluation of PH. Variceal bleeding occurs at HVPG > 12 mmHg or with the appearance of other complications (13); an HVPG > 20 mmHg is a significant prognostic indicator of failure to control bleeding and mortality (10). Reports also suggest that HVPG is the only factor affecting the prognosis of EVB, and it has been demonstrated that there is a significant difference between the bleeding and non-bleeding groups using HVPG ≥ 20 mmHg as a cut-off indicator. In our study, the cases were divided into two groups based on the PPG, and the results showed that the level of EVD was positively correlated with the PPG. Furthermore, the multivariate analysis revealed a significant difference between the two groups. Therefore, this finding indicates that EVD is a predictive factor for adverse events, such as bleeding and poor prognosis, due to increased PPG, especially when EVD exceeds 1.1 cm.

In recent years, there have been significant advancements in the management of EVB, particularly in regard to non-invasive methods to assess the degree of PH, with a focus on the condition of varices. The most direct approach to evaluating EV is through endoscopic examination. The American Association for the Study of Liver Disease recommend endoscopic screening for patients with liver cirrhosis to identify those at a high risk of variceal bleeding (14). Research conducted over a decade ago revealed a correlation between HVPG and the severity of liver disease and the size of varices, demonstrating a significant difference in HVPG between small and large EVs (15). Subsequent studies also confirmed a strong positive correlation between the endoscopic grade of EV and HVPG (16). Another study indicated that EVD could predict early postoperative rebleeding in patients undergoing endoscopic variceal ligation, showing better predictive ability than the grade of EV. However, current reports have not established a relationship between EVD and PPG or HVPG, nor the potential clinical significance of diameter. EVD is a measurable indicator that is easier to quantify compared to the endoscopic grade of EV. The novelty of this study is its first-time description of the relationship between variceal diameter and PPG.

This study offers new insights into non-invasive techniques for measuring PPG, which could not only reduce patient discomfort and medical expenses but also assist clinical practitioners in assessing the severity of patient conditions.

The assessment of the diameter and severity of EV primarily depends on the visual judgment of doctors during endoscopic examinations. This method is subjective and lacks consistency, making it challenging to obtain accurate quantitative measurements. Variations in the diagnosis and grading of EV among different endoscopists have been observed (17).

To enhance data quality and improve the credibility of results, our team developed a non-invasive technology called the Virtual Ruler (VR), supported by artificial intelligence (AI), to measure esophageal variceal diameter (EVD) during endoscopy in previous research (9). This technology has received national utility model patent authorization. The images collected during endoscopy were re-evaluated using the objective measurement

TABLE 3 General material analysis of the two groups of patients.

Factors	PPG < 20 mmHg ($n = 27$)	PPG ≥ 20 mmHg ($n = 101$)	t/Z	P
Age	55.78 ± 11.09	54.82 ± 11.32	0.392	0.696
SBP	104.67 ± 11.10	105.24 ± 9.12	−1.831	0.075
DBP	60.33 ± 8.04	63.47 ± 7.31	−1.937	0.055
EVD	0.60 (0.50, 1.00)	1.20 (1.00, 1.50)	−5.038	0.000
ALB	29.93 ± 6.94	32.01 ± 5.63	−1.624	0.107
Ascites	1 (0, 2)	2 (1, 2)	−2.096	0.036
ALT	23.00 (17.00, 39.00)	25.00 (17.00, 47.50)	−0.678	0.498
BA	44.35 (36.00, 63.75)	49.50 (23.40, 71.95)	−0.296	0.767
PT	16.25 (13.55, 17.62)	15.10 (13.70, 17.20)	−1.069	0.285
WBC	3.09 (2.04, 5.17)	2.31 (1.51, 3.33)	−2.208	0.027
HB	69.00 (61.75, 77.75)	74.00 (63.00, 86.50)	−0.762	0.446
PLT	71.50 (39.75, 89.75)	58.00 (37.25, 74.75)	−1.468	0.142
TBiL	22.80 (16.40, 37.17)	18.80 (14.20, 27.00)	−1.486	0.137
Child-Pugh score	9 (7, 10)	8 (7, 9)	−0.560	0.576
Child-Pugh grade	2 (2, 3)	2 (2, 2)	−0.578	0.564

TABLE 4 Logistic regression analysis.

Factors	P-value	SE	Wald χ^2	P	OR	95%CI
EVD	3.377	0.845	15.978	0.000	29.275	5.590–153.304
ALB	0.038	0.066	0.321	0.571	1.038	0.912–1.182
Ascites	0.372	0.340	1.197	0.074	1.450	0.745–2.823
SBP	−0.013	0.039	0.107	0.744	0.987	0.914–1.066
DBP	0.070	0.057	1.498	0.221	1.073	0.959–1.200
WBC	−0.121	0.142	0.727	0.394	0.886	0.670–1.171
Child-Pugh grade	0.394	0.724	0.297	0.586	1.483	0.359–6.128
TBiL	−0.030	0.021	1.920	0.166	0.971	0.931–1.012

tool, effectively compensating for the subjective judgment of endoscopists. Our previous study demonstrated a correlation coefficient of 0.815 between physician visual assessments and VR measurements of EVD and an intraclass correlation coefficient of 0.965 among the measurements of three physicians using the VR, indicating consistency within and between different groups (8).

The intelligent artificial ruler can accurately measure the diameter of esophageal varices, assess bleeding risk and prognosis in PH, and guide the development of precise endoscopic and clinical treatment plans.

However, several limitations are present in this study. While clinical data were obtained from two medical centers, further validation will require data from additional institutions and larger sample sizes. Furthermore, since the clinical cases included only patients treated for bleeding events through endoscopic or interventional methods, the PPG levels were relatively high. This made it challenging to establish a relationship between EVD and PPG, particularly at lower PPG levels.

Increasing the number of cases with PPG < 20 mmHg may require the inclusion of primary prevention cases. However, conducting invasive PPG examinations may not adhere to ethical standards and could potentially harm patients, leading to increased anxiety and concern. We will continue our research and collect additional samples. It is also important to note patients with PPG < 20 mmHg have a lower risk of bleeding and a better prognosis, suggesting that those with higher PPG levels may require more focused attention.

In future studies, we will examine the relationship between EVD and the risk of rebleeding. Preliminary results indicate that patients with a diameter exceeding 1.1 cm have a higher rebleeding rate compared to those with smaller diameters. This finding can help develop more effective clinical strategies and improve patient outcomes. We recommend regular endoscopic interventions for patients with a diameter greater than 1.1 cm.

In conclusion, the findings indicate that EVD is associated with PPG levels. In patients with liver cirrhosis, an EVD greater than 1.1 cm detected endoscopically or over 1 cm observed visually may

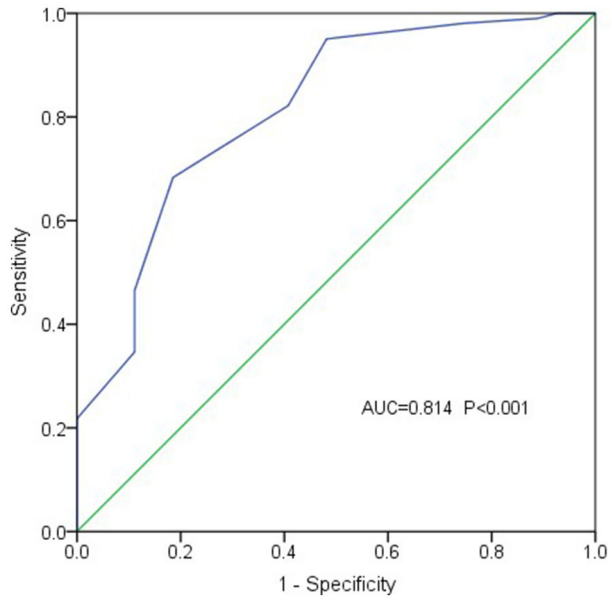

FIGURE 3
The ROC curve demonstrated that the EVD was effective in diagnosing PPG (PPG ≥ 20 mmHg).

suggest a PPG exceeding 20 mmHg. Measuring EVD may provide a novel, non-invasive approach to assessing PPG and offer additional insights to aid in identifying adverse events linked to elevated PPG.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were both approved by the Committee on Medical Ethics of the First Affiliated Hospital of Anhui Medical University or the Medical Research Ethics Committee of the First Affiliated Hospital of USTC. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YM: Data curation, Formal analysis, Methodology, Writing – review & editing, Writing – original draft. ZF: Data curation, Writing – review & editing. YH: Formal analysis, Writing – review & editing. JJ: Validation, Writing – review & editing. XD: Data curation, Validation, Writing – review & editing. DK: Methodology, Supervision, Validation, Data curation, Writing – review & editing.

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Conflict of 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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Commonly encountered symptoms and their management in patients with cirrhosis

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This exhaustive review, explored the multifaceted symptoms and their management in patients with cirrhosis. Patients frequently endure pain, muscle cramps, sleep disturbances, psychological distress, and gastrointestinal issues, significantly impairing their quality of life. Pain is prevalent, often requiring analgesics, while muscle cramps affect up to 68% of patients, treated with supplements like zinc and taurine despite limited evidence. Sleep disturbances, including insomnia and excessive daytime sleepiness, afflict up to 80% of patients, managed through lactulose, melatonin, and cognitive behavioral therapies. Gastrointestinal symptoms, affecting 80%, include abdominal pain and bloating, necessitating lifestyle and dietary adjustments. Mental health disorders, such as depression and anxiety, are common, managed with a combination of pharmacotherapy and psychotherapy. Sexual dysfunction, often overlooked, profoundly impacts both men and women, requiring holistic treatment approaches. Pruritus, another distressing symptom, is managed with moisturizers and antihistamines, though many treatments show limited success. Hair loss and skin changes add to the psychological burden, highlighting the need for a comprehensive, multidisciplinary approach. The review underscores the imperative for tailored, compassionate care to enhance patient outcomes and quality of life in cirrhosis.

KEYWORDS

muscle cramps, insomnia, pruritus, depression, portal hypertension, decompensated cirrhosis

1 Introduction

Cirrhosis represents the advanced stage of chronic inflammatory liver damage, marked by the disruption of intrahepatic vasculature, hepatocyte loss, and extensive scarring. This leads to the formation of regenerative hepatic nodules encased in dense fibrous tissue, containing significantly higher levels of extracellular matrix proteins, particularly collagen types I, III, and IV, which hinder portal blood flow and elevate portal pressure, ultimately culminating in clinically significant portal hypertension in later disease stages (1). Progression through various disease stages in cirrhosis is fraught with complications related to portal hypertension and chronic liver failure, such as acute variceal bleeding, ascites, hydrothorax, hepatic encephalopathy (HE), life-threatening infections, and extrahepatic organ failure, such as hepatorenal syndrome and additionally, hepatocellular carcinoma (2). Although the management of these complications is well-delineated in clinical guidelines based on robust interventional trial data and are major reasons for hospitalizations, certain symptoms significantly impacting quality of life often prompt recurrent outpatient and emergency visits among individuals with cirrhosis.

These encompass a spectrum of maladies including malaise, fatigue and lethargy, appetite disturbances, non-cholestatic pruritus, muscle cramps, sleep disturbances, mental health disorders, gastrointestinal symptoms, sexual dysfunction, pain and peripheral neurological symptoms, hair loss and self-consciousness inducing skin changes. In general, the most frequently reported symptoms in cirrhosis include: pain (prevalence range 30–79%), breathlessness (20–88%), muscle cramps (56–68%), sleep disturbance (insomnia 26–77%, daytime sleepiness 29.5–71%), psychological symptoms (depression 4.5–64%, anxiety 14–45%), and erectile dysfunction (53–93%) in men (3, 4). Regrettably, these symptoms, which exact a financial and resource burden on both patients and healthcare systems, are not currently addressed in guideline-based treatment recommendations.

In this comprehensive and evidence-driven review, the objective is to scrutinize the repercussions, diagnosis, and management of these often overlooked yet prevalent and challenging-to-treat symptoms encountered in cirrhosis (Figure 1). By disseminating current best practices, the review endeavors to equip physicians caring for patients with liver disease with the requisite knowledge to optimize patient care.

2 Cirrhosis-related malaise, fatigue, or lethargy

2.1 Definitions and prevalence

Malaise embodies a pervasive sense of discomfort, weakness, or unease, the precise origin of which proves elusive and closely intertwines with mental well-being (5). Conversely, fatigue denotes an overwhelming sensation of tiredness and depleted energy levels that hinder the individual's customary activities (6). However, lethargy constitutes a more profound manifestation of illness-associated symptoms, characterized by profound drowsiness, extreme lethargy, and cognitive dullness (7). Individuals afflicted with cirrhosis commonly exhibit one or a combination of these symptoms, collectively termed as the non-specific symptom complex or "sickness behaviors," significantly impacting their quality of life, daily functioning, mental well-being, and productivity. The prevalence of fatigue in cirrhosis exhibits considerable variability across studies, populations, and etiologies, with the definitive prevalence of this condition remain uncertain. Nonetheless, reported prevalence rates range from approximately 60 to 80% in various investigations (4, 7, 8). In contrast, the prevalence of fatigue stands at around 5% in the

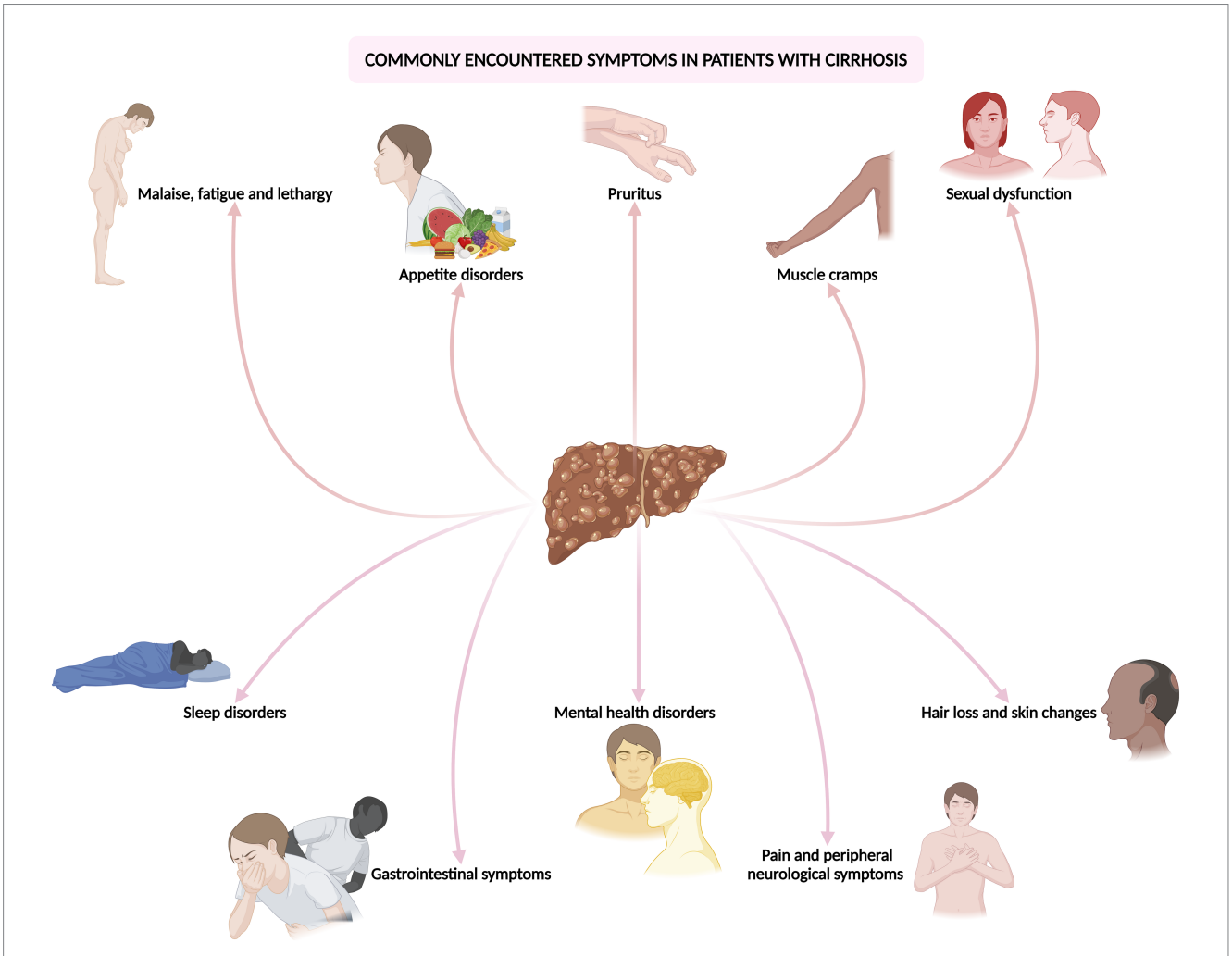

FIGURE 1
Common symptoms encountered in the outpatient and emergency department in patients with cirrhosis.

general population and approximately 20% in non-cirrhotic community settings (9). Although fatigue prevalence fluctuates concerning cirrhosis etiology, ranging from 44% in autoimmune liver disease to as high as 80% in primary biliary cholangitis (7), it is noteworthy that this symptom may not necessarily correlate with the severity of underlying liver fibrosis, advanced disease stages, or organ dysfunction.

2.2 Mechanism and causes

Muscle functionality and contractility can suffer impairment either at or beyond the neuromuscular junction, termed peripheral fatigue, or proximal to it, referred to as central fatigue. Notably, fatigue observed in cirrhosis predominantly aligns with the central type. The pathophysiology is intricate, multifaceted, and consequently poorly elucidated. Disrupted peripheral neurogenic signaling pathways between the liver and the brain axis, coupled with perturbed central neurotransmission within the brain, in tandem with disease-related or disease-associated factors, such as complications, treatments, and severity, as well as alcohol use, metabolic syndrome, and malignancy, collectively contribute toward clinical fatigue (10). The interplay of local (within the diseased liver) and systemic inflammation, stemming from portal hypertension and alterations in the gut microbiome, alongside heightened levels of circulating cytokines, disrupts hepatic vagal neurogenic responses and impacts cerebral endothelial cells, giving rise to neuroinflammation. This intricate nexus, predominantly involving peripherally activated immune cells, notably circulating monocytes, and microglia, along with its repercussions on signaling pathways like serotonin, dopamine, and corticotropin-releasing hormone, with the latter's implications on the hypothalamus-pituitary–adrenal axis, initiates sickness behaviors, including fatigue (4, 8). Moreover, the presence of diminished muscle mass and power, aberrant muscle quality characterized by increased fat or myosteatosis, electrolyte imbalances, malnutrition, subclinical myopathy, diminished motivation, memory, and concentration, alongside an array of mental health and sleep disorders directly linked to or associated with the underlying disease, further exacerbate, and contribute to fatigue in cirrhosis (9).

2.3 Diagnosis and management

Peripheral fatigue can be quantified through objective assessments of strength and aerobic capacity, while central fatigue is evaluated using self-reports and validated questionnaires that capture the patient's perception of physical and mental exertion impacts on their activities and exertion levels. Peripheral fatigue can be measured with tests such as hand-grip strength, short physical performance battery, cardiopulmonary exercise testing, and the 6-min walk test. Central fatigue, on the other hand, is assessed using tools like the visual analog scale, patient-reported outcomes measure information system for fatigue, fatigue severity scale, and fatigue assessment scale (8–10). Diagnosing pathological fatigue necessitates the significant presence of fatigue, reduced energy, and a disproportionate need for rest relative to activity levels. Additionally, at least five ancillary symptoms must be present, such as limb heaviness or generalized weakness, diminished concentration, or attention, decreased motivation or interest in usual activities, insomnia or hypersomnia, nonrestorative sleep, perceived need to struggle against inactivity, pronounced emotional response to fatigue, perceived short-term memory issues, or prolonged malaise following exertion (11).

Managing fatigue in cirrhosis encompasses both non-pharmacological and pharmacological strategies. Non-pharmacological approaches involve addressing the underlying causes of cirrhosis and adhering to the validated TrACE (Treating causes, Ameliorating modifiable factors, Coping mechanisms, and Empathizing) model, particularly used to manage fatigue in primary biliary cholangitis. This model emphasizes treating causes such as electrolyte imbalances, various types of anemia (including screening for testosterone deficiency related anemia), and vitamin and mineral deficiencies, as well as managing comorbidities like metabolic syndrome and glucose control. Patients are educated on avoiding triggers such as shift work, alcohol, tobacco, prolonged bed rest, weight gain, lack of sleep, and stress, while promoting strategies to manage fatigue including increasing exercise, consuming nocturnal protein snacks, and employing ergogenic nutrition (2, 4, 9).

Pharmacological treatments, however, have shown limited evidence of effectiveness in alleviating fatigue. Several drugs have been studied, but none have demonstrated significant benefits, indicating a need for larger, well-designed, controlled trials. These drugs include ondansetron (small benefit in a small randomized trial), S-adenosyl-methionine (SAMe, small benefit in uncontrolled studies), pentoxifylline (no benefit), modafinil (no benefit), hydroxyzine, zolpidem, trazodone, and melatonin (no benefit for sleep quality and insomnia) (8, 9).

In conclusion, non-pharmacological therapies that focus on controlling the etiology of liver disease, improving nutrition, increasing muscle mass, mitigating triggers and risk factors, and enhancing coping mechanisms are significantly more effective in combating fatigue in cirrhosis compared to pharmacological treatments (Figure 2) (4, 9).

3 Cirrhosis-related appetite disorders, restrictive diet, and malnutrition

3.1 Prevalence, risk factors and mechanisms

Chronic liver failure in end-stage cirrhosis often leads to low appetite, nutritional deficits, and malnutrition. Decompensated cirrhosis patients frequently report low appetite during outpatient visits, with malnutrition affecting 50–90% of those with advanced cirrhosis (12). Appetite issues in cirrhosis, including decreased food intake and quality, stem from various factors. Clinical complications related to liver failure and portal hypertension, such as hepatic encephalopathy, symptomatic ascites, repeated hospitalizations, medication burden, electrolyte imbalances (especially hyponatremia), low sodium diets, and general debility, exacerbate appetite loss (13). A small study found that over one-third of cirrhosis patients experienced reduced appetite (14). Chemosensory dysfunctions in chronic liver disease patients alter smell and taste, affecting appetite and leading to nutritionally inadequate food cravings and preferences (15). Inflammation-associated anorexia, prevalent gastrointestinal symptoms due to slow intestinal transit, disrupted appetite regulation, and energy expenditure—linked to overexpression of leptin, increased bound leptin, irregular ghrelin secretion, and blunted ghrelin responses—correlate with liver disease severity and systemic

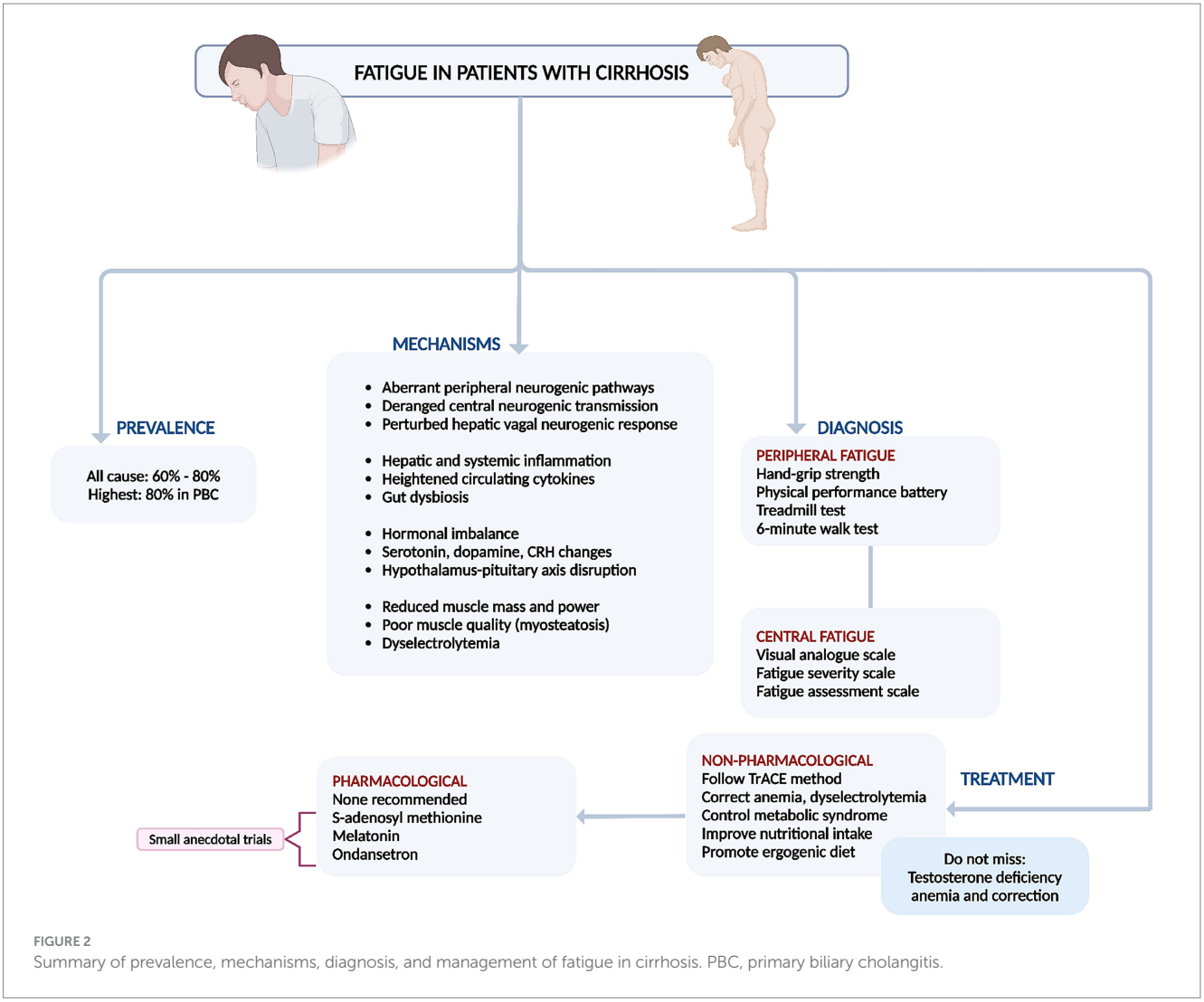

FIGURE 2
Summary of prevalence, mechanisms, diagnosis, and management of fatigue in cirrhosis. PBC, primary biliary cholangitis.

inflammation, further reducing food intake quantity and frequency of spontaneous food consumption (12, 16). Additionally, advanced cirrhosis patients often experience abdominal symptoms such as pain and reflux, and are sarcopenic, a factor independently associated with mortality (13). Currently, there are no validated guidelines for assessing appetite disorders in cirrhosis, highlighting an unmet need to identify those at risk of liver-related complications and malnutrition. However, the Simplified Nutritional Appetite Questionnaire (SNAQ) may be useful in identifying patients with poor appetite and at risk of unhealthy weight loss and malnutrition (17).

3.2 Treatment

It is crucial to address the patient holistically by managing risks and triggers, rather than relying only on pharmacological treatments. There is currently no evidence that "appetite enhancers" effectively improve symptoms or increase nutritional intake in cirrhosis patients. Treating low appetite in advanced cirrhosis should focus on addressing risk factors (such as active alcohol use, uncontrolled diabetes, and hypothyroidism), triggers (including hepatic encephalopathy, infections, electrolyte imbalances, and excessive medication burden), and related issues (such as removing symptomatic ascites, providing clear dietary recommendations, avoiding overly restrictive diets, and addressing mental health concerns) (13, 18). International guidelines recommend a sodium intake restriction of 2,000 mg/day for patients with decompensated cirrhosis. However, simplistic advice to "avoid salt" and processed foods, combined with misguided traditional dietary advice (such as avoiding whole eggs, dairy, animal-based proteins, oils, and fats), can lead to avoidant-restrictive food intake disorder (19). This negatively impacts both mental health and appetite due to fearmongering and confusion about nutritional choices. Sodium restriction alone alleviates ascites in only about 10–15% of patients, and some studies show no additional benefit over an unrestricted diet when diuretics are used, if sodium intake adheres to recommended levels. Enhancing food palatability with a diverse, patient-tailored diet that avoids added salt and ensures well-spaced diet intake could help mitigate appetite disorders in cirrhosis (18). Taste changes (dysgeusia), a common issue in cirrhosis, contribute to low appetite. Zinc and vitamin A, which are essential for maintaining taste integrity and often deficient in advanced cirrhosis, should be identified and corrected to improve appetite and food palatability in these patients (Figure 3) (13, 18).

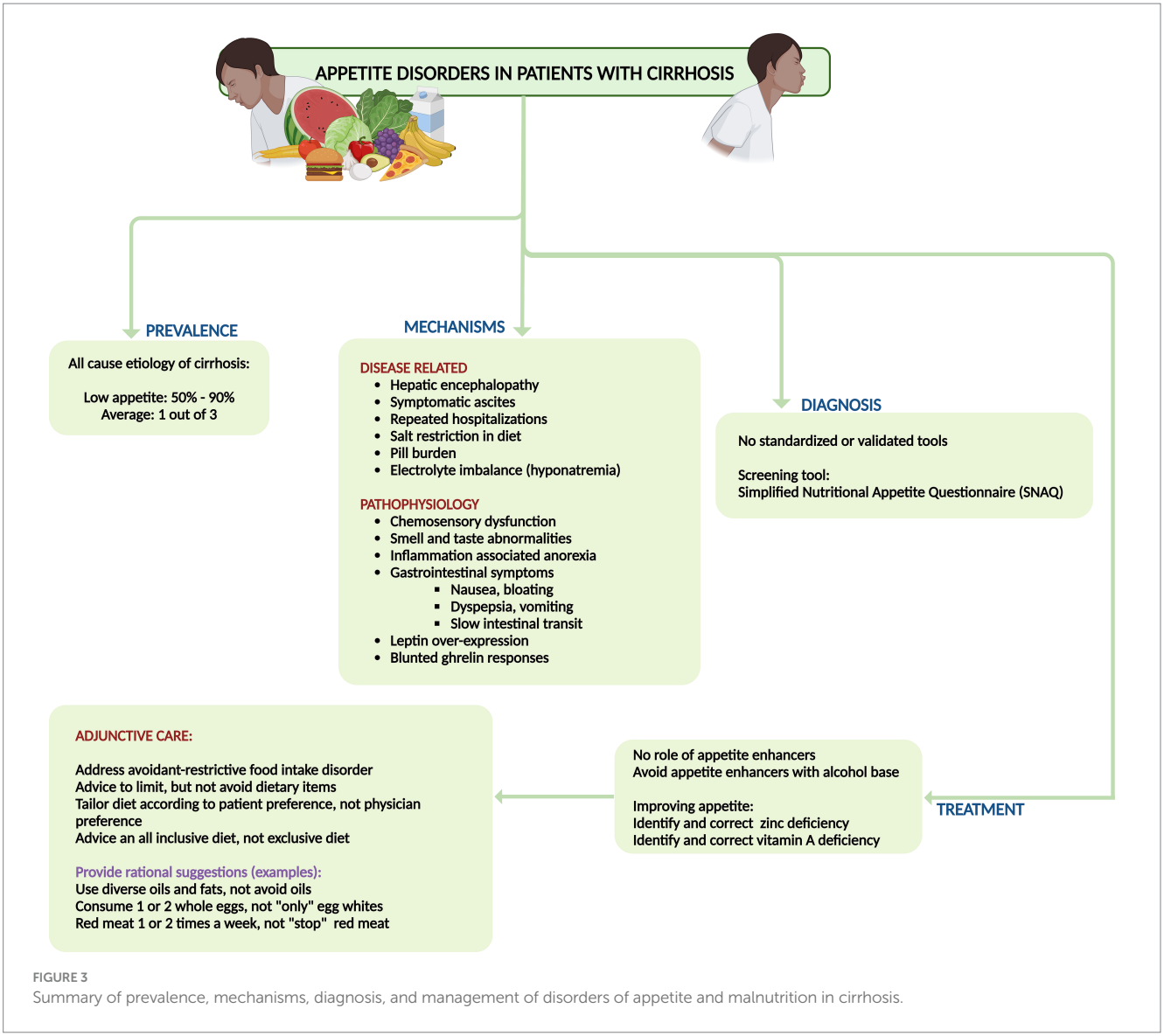

FIGURE 3
Summary of prevalence, mechanisms, diagnosis, and management of disorders of appetite and malnutrition in cirrhosis.

4 Cirrhosis-related non-cholestatic pruritus

4.1 Prevalence and mechanisms

Pruritus linked to liver ailments is particularly pronounced in chronic cholestatic liver conditions like primary biliary cholangitis and primary sclerosing cholangitis. While the treatment for pruritus stemming from cholestatic liver disorders is established, pruritus originating from non-cholestatic causes is frequently encountered in cirrhotic patients due to various non-cholestatic factors. The prevalence of pruritus varies depending on the underlying cause, with reports indicating rates of up to 70% in primary biliary cholangitis, 2.5–30% in chronic hepatitis C virus-related liver disease, and roughly 8% in cirrhosis attributed to hepatitis B virus infection (20). Pruritus in cirrhosis typically affects larger body areas such as the back and abdomen, sparing smaller extremities like the soles and palms, hands, and feet. It tends to intensify during daytime rather than nighttime, with exacerbations commonly occurring during the winter season and cold climates (20, 21). Factors such as severe thrombocytopenia, serum aspartate aminotransferase levels exceeding 60 U/L and the presence of diabetes have been identified as independent predictors associated with pruritus in cirrhosis (21).

Numerous hypotheses have been posited to elucidate the genesis of pruritus, albeit none deemed definitive. These include heightened endogenous opioid production and the activation of μ-opioid receptors, instigating itching by attenuating pain signaling. Additionally, elevated levels of circulating bile acids and dysregulated synthesis of lysophosphatidic acid and autotaxin are implicated. Pruritus characteristic of cirrhosis predominantly manifests as a central phenomenon, purportedly stemming from augmented release of β-endorphin, Met-enkephalin, and endomorphin-1,2, which stimulate μ-receptors within nerve tissues. Conversely, in the peripheral variant, histamine discharge from mast cells triggers the activation of itch receptors at the epidermal-dermal interface. The pruritus associated with cirrhosis exacts a toll on quality of life, exacerbates sleep disturbances and mental health disorders including suicidal ideation, and serves as a primary driver of recurrent outpatient consultations.

4.2 Diagnosis and treatment

The crucial first step in diagnosing the root cause of itching demands a meticulous investigation into the presence of a rash, a potential pointer to dermatologic cause. Should this prospect be dismissed, an exhaustive exploration of other potential culprits is imperative, including systemic causes (both hepatic and extrahepatic), neurological disorders, and psychogenic triggers (20). The localization of itching implies an origin rooted in either neurological dysfunction or psychogenic factors. A comprehensive medical history is paramount, delving into risk factors for liver disease, existing medical comorbidities, general symptoms, and the utilization of medications or substances. Employing patient questionnaires at the outset and throughout treatment serves as a valuable tool for assessing the gravity of itching and tracking therapeutic responses. Various standardized scales, such as the Numerical Rating Scale, Dermatology Life Quality Index, and 5D Itch Scale, serve as objective metrics in clinical settings, evaluating diverse facets of itching encompassing its intensity, distribution, and associated conditions like anxiety, depression, and insomnia, along with overall quality of life (22). In instances suggestive of biliary obstruction, the deployment of imaging modalities such as ultrasound or cross-sectional imaging is warranted.

There are no recommended pharmacological therapies for control of pruritus in cirrhosis. The armamentarium includes various medications that are tailored toward patient tolerability and considering underlying liver disease severity. Skin changes and temperature dysregulation leading to loss of turgor, dryness and therefore itching and surface breaks are common in cirrhosis and the use of moisturizers to improve hydration and maintain barrier integrity is always the first step toward reducing pruritus (4). Antihistamines like hydroxyzine and diphenhydramine are frequently employed as initial treatments for pruritus due to their safety and availability. However, their efficacy data are limited, and their sedative effects can potentially induce hepatic encephalopathy in patients with chronic liver failure. Furthermore, hydroxyzine can prolong the QT interval, potentially leading to fatal torsades de pointes. It is crucial to recognize that patients with cirrhosis often experience electrolyte imbalances, making them particularly susceptible to QT interval prolongation (4, 8). Ursodeoxycholic acid (UDCA) has been found ineffective for pruritus relief in primary sclerosing cholangitis and primary biliary cholangitis but is recommended for treating pruritus in intrahepatic cholestasis of pregnancy only, at doses of 10–15 mg/kg/day, divided into 2–3 doses. There is no evidence supporting its benefit in non-cholestatic pruritus associated with cirrhosis (4, 20). Cholestyramine, a bile salt resin, effectively alleviates cholestatic pruritus and is the first-line treatment even in cirrhosis due to its general tolerability and safety (4). Potential gastrointestinal side effects include constipation and, rarely, fat malabsorption. Dosages range from 4 g once or twice daily, up to a maximum of 16 g/day in divided doses (4, 8, 20). Other medications should be administered either 1 h before or 4–6 h after cholestyramine intake to avoid interaction. Rifampicin has shown effectiveness in alleviating cholestatic pruritus but poses a hepatotoxicity risk in up to 13% of patients with prolonged use and has not been studied for pruritus in cirrhosis (4, 23). Naltrexone, a μ-opioid receptor antagonist, dosed at 25–50 mg daily, has demonstrated efficacy in small trials for treating cholestatic pruritus. However, it is contraindicated in patients with chronic liver failure due to concerns about hepatic encephalopathy and associated symptoms like malaise, nausea, appetite loss, and abdominal cramps (23). Sertraline has shown moderate effectiveness in reducing pruritic symptoms and is generally well-tolerated. However, it should be used cautiously in patients with advanced liver disease and is generally not recommended (8, 23). A 2021 study on nalfurafine, a κ-opioid agonist metabolized by cytochrome P450 into an inactive form, showed significant improvement in pruritus scores without notable adverse effects at doses of 2.5 mg and 5 mg, regardless of daytime or nighttime itching (24). A summary of treatment options for pruritus in cirrhosis is shown in Figure 4.

5 Muscle cramps

5.1 Prevalence and mechanisms

Muscle cramps are involuntary, at times visible, and painful contractions of skeletal muscles that can occur at rest or be intense enough to awaken a person from sleep. Muscle cramps can endure from a few seconds to several minutes, often causing lasting tenderness and swelling for up to 72 h after an episode. They predominantly occur at night, leading to significant sleep disturbances. Muscle cramps are an independent risk factor for diminished health-related quality of life. They disrupt sleep, hinder physical functioning and mobility, and negatively impact general and mental health (25). The prevalence of muscle cramps in liver cirrhosis varies widely, ranging from 29 to 88% depending on the investigators' inclusion criteria. Recent studies comparing cirrhosis and chronic hepatitis revealed that muscle cramps were significantly more common in cirrhosis patients (51.8–52.0%) than in those with chronic hepatitis (7.5–43.7%). Muscle cramps predominantly afflict the lower limb muscles, notably the calves and feet, though the fingers and hands may also be susceptible (4, 8, 26). The prevalence of cramps among individuals with chronic liver disease spans from 22 to 88%, mirroring the incidence observed in other chronic conditions such as type 1 diabetes mellitus (24–34%), type 2 diabetes mellitus (45–78%), and chronic kidney disease (56–67%), yet markedly exceeding that of the general populace. Factors such as female sex, concomitant diabetes, and chronic kidney disease were linked with the occurrence of muscle cramps in chronic liver disease. Additionally, diminished muscle mass was associated with muscle cramps in nonalcoholic fatty liver disease (27). These findings indicate that muscle cramps in cirrhosis are independently associated with the severity of the liver disease and declining liver function.

The precise pathophysiology of muscle cramps persists in its obscurity, and efficacious treatments have yet to be ascertained. Researchers discerned no correlation between the incidence of muscle cramps and factors such as edema, ascites, diuretic use, alcohol consumption, but have identified the presence of liver cirrhosis, higher total serum bilirubin levels, and lower serum albumin levels as risk factors for development of muscle cramps (25, 28). The etiology of muscle cramps is complex and multifactorial. Hyperexcitability of motor nerve terminals can be incited by disrupted energy metabolism, ischemic damage resulting from reduced intravascular volume, and electrolyte imbalances. Oxidative stress, along with structural changes such as axonal loss and demyelination from toxic insults like hyperglycemia and alcohol consumption, are also associated factors. In cirrhosis, decreased adenosine triphosphate production in muscles can cause ion channel dysfunction and destabilization of the sarcolemma, leading to prolonged muscle contractions. Studies have revealed no significant differences in electrolyte

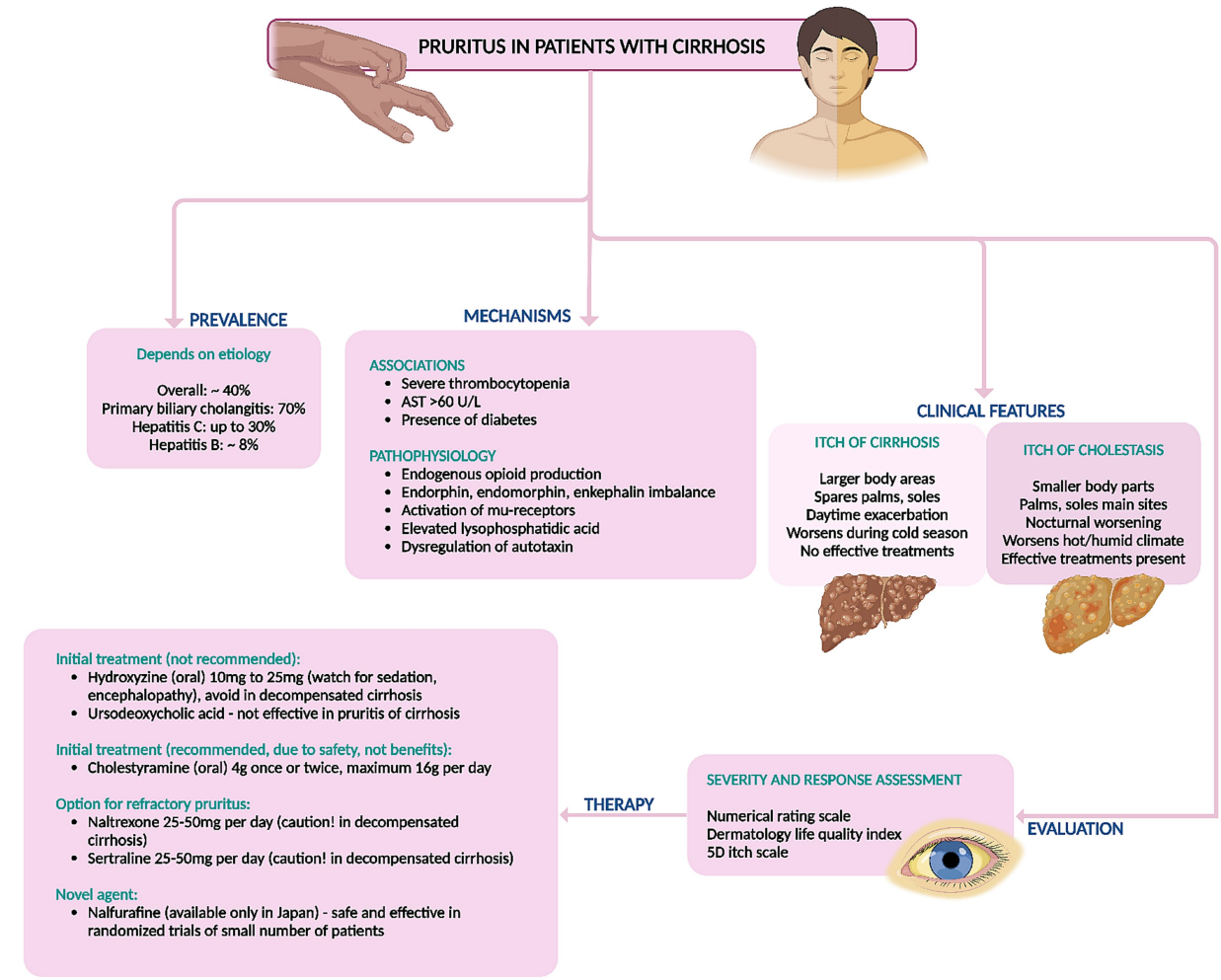

FIGURE 4
Summary of prevalence, mechanisms, diagnosis, and management of non-cholestatic itching (pruritus) in cirrhosis. AST, aspartate aminotransferase.

concentrations, diuretic use, or liver disease severity among patients experiencing muscle cramps. However, shifts in plasma volume play a pivotal role, as the presence of ascites, lower mean arterial pressure, and higher plasma renin activity have been identified as key predictors of muscle cramps (29). Even though severe magnesium deficiency has been unequivocally linked to muscle cramping, as magnesium is believed to mitigate muscular excitability, studies found no correlation between serum magnesium levels and the occurrence of muscle cramps in patients with cirrhosis (25, 28).

5.2 Treatment

The therapeutic arsenal for alleviating muscle cramps in cirrhosis spans a variety of agents, including vitamin E, pregabalin, intravenous albumin, eperisone, taurine, zinc, baclofen, methocarbamol, orphenadrine, branched-chain amino acids, L-carnitine, and quinidine. The efficacy of these medications has largely been evaluated through small cohort studies and uncontrolled case series, rendering them less recommended for treating muscle cramps comprehensively (25, 28). Vitamin E (200 mg thrice daily for 4 weeks) demonstrated significant improvement in a limited case series; however, a subsequent double-blinded, placebo-controlled trial failed to replicate these benefits and even noted exacerbation in some instances. L-carnitine, crucial in fatty acid metabolism and often deficient in cirrhosis patients, significantly mitigated cramps at doses ranging from 300 mg twice daily to 1,200 mg/day. Supplementation coupled with exercise proved advantageous, with no adverse events reported, albeit in small, uncontrolled studies. Zinc supplementation (220 mg twice daily for 12 weeks) showed efficacy in a minor study, notwithstanding one case of diarrhea. Notably, zinc levels did not correlate with cramp occurrence. Taurine, a nonessential amino acid, effectively reduced muscle cramps in cirrhosis patients. Studies administering 3 gm/day to 6 gm thrice daily over 1 to 24 months reported significant improvements, corroborated by recent trials with doses up to 2 gm/day without adverse effects. Vitamin D supplementation (0.5–1.0 μg for 2 weeks) reduced cramps in about half of the patients, though no RCTs have been conducted. Branched-chain amino acid levels, typically reduced in cirrhosis patients, were restored through supplementation, which alleviated muscle cramps, particularly with higher and nocturnal

doses, yielding minimal self-limiting adverse events. Baclofen, a muscle relaxant, demonstrated substantial reductions in cramp severity and duration, with a small randomized controlled trial confirming its efficacy and tolerability. Pregabalin, for neuropathic pain, significantly decreased cramp frequency versus placebo, though pain intensity during sleep remained unaffected. It was well tolerated. Methocarbamol (500 mg twice daily) reduced cramp frequency and severity with no severe side effects, though benefits diminished post-cessation. Orphenadrine (100 mg twice daily), an anticholinergic, significantly reduced cramp frequency, severity, and duration, as supported by a placebo-controlled trial with minimal side effects. Intravenous albumin lowered cramp frequency in a randomized cross-over trial, warranting further investigation. Quinidine (400 mg/day) reduced cramp incidence by 88% versus 13% with placebo, though some patients experienced diarrhea. Eperisone hydrochloride (150–300 mg/day) also reduced cramp frequency, with common side effects including fatigue and dizziness (25, 28, 29).

Importantly, none of these clinical trials were adequately powered, well-designed, or replicated to confirm the efficacy of these interventions conclusively. Among these, taurine (500–1,000 mg/day) for prevention stands out with relatively better evidence. Additionally, the utility of pickle juice sips at cramp onset has shown promise in ameliorating acute cramps (Figure 5) (30).

6 Sleep disorders in cirrhosis

6.1 Prevalence, characteristics, and mechanisms

Sleep disturbances worsen quality of life in cirrhosis, demanding vigilant management to uplift health-related quality of life (HRQoL) and clinical outcomes. Up to 80% of cirrhosis patients report poor sleep quality, as evidenced by Pittsburgh Sleep Quality Index (PSQI) scores exceeding 5 (Child–Turcotte–Pugh [CTP] A: 16.9%, CTP B: 26.5%, and CTP C: 56.6%), and around 16 to 52% suffer from excessive daytime sleepiness (EDS), reflected by Epworth Sleepiness Scale (ESS) scores over 10 (CTP A: 17.6%, CTP B: 29.7%, CTP C: 52.8%) (31). Studies have indicated that 47% of cirrhosis patients endure sleep disturbances, while 69% experience both disturbed sleep and depression. Among those with end-stage liver disease, approximately 81% grapple with sleep disorders, often attributed to HE (32). The relationship between sleep quality and cirrhosis severity is complex; some studies reveal a dose–response link, while others do not. Patients with cirrhosis frequently show increased sleep latency, diminished sleep maintenance and efficiency, alongside altered rapid-eye-movement (REM) sleep patterns. Common sleep disorder phenotypes in cirrhosis include insomnia, EDS,

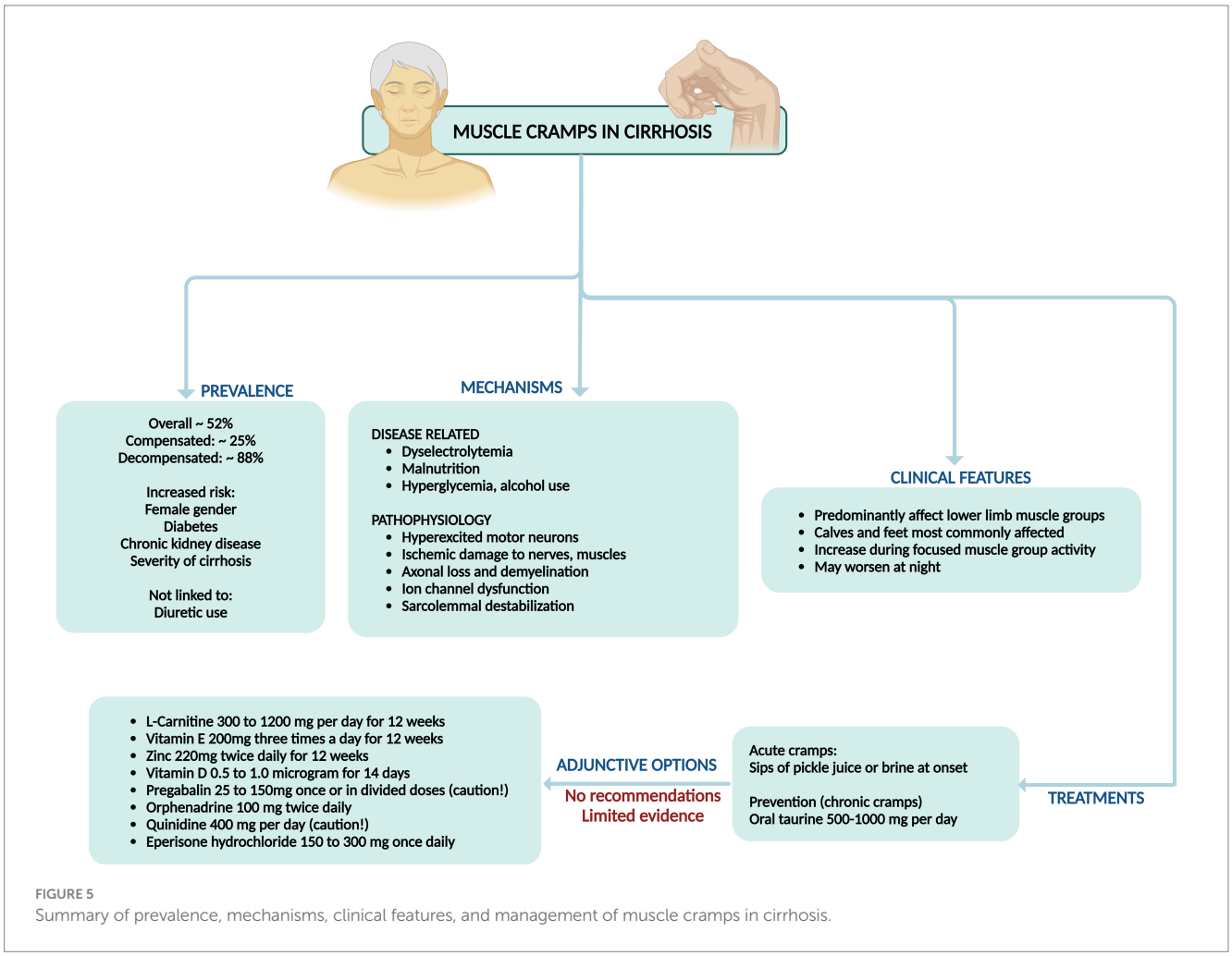

FIGURE 5
Summary of prevalence, mechanisms, clinical features, and management of muscle cramps in cirrhosis.

obstructive sleep apnea (OSA), and restless leg syndrome (RLS) (31).

Insomnia, defined as difficulty initiating or maintaining sleep, is chiefly diagnosed through patient-reported symptoms. Cirrhosis patients describe it as an inability to fall asleep, fragmented sleep, frequent nocturnal awakenings, and overall poor sleep quality, impairing daytime functioning. Observational studies reveal that insomnia affects 42–65% of cirrhosis patients. Notably, insomnia prevails even in well-compensated cirrhosis stages and is not linked to neuropsychiatric impairment. Research indicates a higher prevalence of insomnia in hepatitis C patients compared to those with hepatitis B or other causes. Insomniac cirrhotics tend to be older and have larger neck circumferences, though no correlation with body mass index has been found (33). Excessive daytime sleepiness is a significant concern among cirrhosis patients with sleep disorders, affecting 21–50% of cases. Studies uncover a robust association between EDS and HE, with 38% of cirrhosis patients experiencing EDS, 89.5% of whom also manifest overt HE. EDS is closely linked to severe cirrhosis and the neuropsychiatric impairments seen in HE (34). Obstructive sleep apnea, caused by upper airway obstruction leading to chronic intermittent hypoxia, maintains a well-documented bidirectional relationship with metabolic syndrome-associated steatotic liver disease (MASLD). It is prevalent in 35–45% of patients with obesity and MASLD due to shared metabolic alterations and comorbidities. Additionally, cirrhosis and viral hepatitis patients show a higher incidence of OSA compared to control groups and patients with severe symptomatic ascites develop sleep disturbances due to secondary OSA (35).

Restless leg syndrome, characterized by an irresistible urge to move the legs during rest accompanied by unpleasant sensations, affects 26.1–55.0% of cirrhosis patients, further disrupting sleep. One study showed that the prevalence was 62% compared to 10% in the general population. The prevalence rates of RLS in cirrhosis vary, with higher rates reported in the United States and Europe compared to Asia (36). Sleep disturbances detrimentally impact HRQoL, correlating with higher mortality and hospitalization rates. Frailty, prevalent in cirrhosis, is linked to increased disease progression and mortality. Poor sleep quality is strongly associated with frailty. Sleep disturbances predict malnutrition and correlate with sarcopenia. Furthermore, sleep disorders in cirrhosis are closely related to HE, with overlapping mechanisms such as disrupted sleep patterns and hyperammonemia (37).

Sleep–wake abnormalities in cirrhotic patients can be attributed to several pathophysiological mechanisms. Delayed sleep onset is linked to decreased melatonin clearance, delayed melatonin peaks, increased melatonin levels during daytime and altered circadian variation of core body temperature. Excessive daytime sleepiness is primarily associated with HE. Short total sleep time, low sleep efficiency, and frequent awakenings are also related to HE, as well as increased interleukin-6 levels, glucose level fluctuations, and low ghrelin values. These disruptions collectively contribute to the compromised sleep health observed in cirrhotic patients (31, 34).

6.2 Assessment and treatment

Sleep disturbances in cirrhosis patients can be evaluated by assessing night sleep quality, sleep–wake timing, and daytime sleepiness. The methods for evaluating sleep–wake behavior in these patients is diverse and can be categorized into subjective and objective/semi-quantitative approaches. Subjective methods for evaluating sleep disturbances encompass daily sleep diaries and retrospective questionnaires. Despite the absence of specific protocols for cirrhosis patients, sleep diaries are heralded as the "gold standard" for subjective sleep assessment (31). Carney et al. crafted the "Consensus Sleep Diary," available in three variations: the "Core Consensus Sleep Diary" with nine essential items, the "Expanded Consensus Sleep Diary for Morning" (CSD-M), which includes early morning awakenings, napping, and substance use, and the "Expanded Consensus Sleep Diary for Evening" (CSD-E) that organizes items for both morning and evening entries (38). The Pittsburgh Sleep Quality Index (PSQI) reigns as the most widely used questionnaire, gaging sleep quality over the past month through 19 items divided into seven components, classifying individuals as "good sleepers" or "poor sleepers" based on a threshold score of 5. The Sleep Timing and Sleep Quality Screening Questionnaire (STSQS) serves as a more concise alternative to the PSQI, providing a rapid assessment that correlates significantly with PSQI outcomes. The Epworth Sleepiness Scale (ESS) measures daytime somnolence across eight scenarios, with scores of 11 or higher denoting excessive daytime sleepiness (EDS). The Basic Nordic Sleep Questionnaire (BNSQ), comprising 27 items, evaluates various sleep complaints and has been employed in studies involving liver transplant recipients and cirrhosis patients. The STOP-Bang questionnaire, with eight items, screens for obstructive sleep apnea (OSA), with scores of 3 or above indicating moderate to severe OSA. Similarly, the Berlin questionnaire (BQ) assesses OSA risk, with a reported 42% risk in cirrhotic patients. Lastly, the International Restless Leg Syndrome Study Group rating scale (IRLSS) appraises the presence and severity of RLS and is a valuable tool specifically in patients with primary biliary cholangitis (31, 33, 36).

Objective methods for sleep disorders assessment in cirrhosis include the polysomnography test which stands as the gold standard for diagnosing sleep disturbances, but its practicality is hindered by high costs and patient compliance challenges. Consequently, alternative assessment methods are often employed. Sleep logs, which track sleep patterns over a minimum of 2 weeks, provide valuable insights. Actigraphy, a portable and cost-effective option, offers a viable alternative to polysomnography, albeit with less accuracy (31–33).

Despite the high prevalence of sleep disturbances among patients with liver cirrhosis, the paucity of routine sleep quality assessments in clinical practice has left a gap in effective management strategies. Current therapeutic options span both pharmacological and behavioral realms. To achieve effective treatment, it is imperative to regularly evaluate nighttime sleep quality and daytime sleepiness using instruments such as the PSQI and the ESS. Lactulose, which lower blood ammonia levels, have demonstrated efficacy in enhancing various sleep parameters even in the absence of overt HE. For example, a three-month course of lactulose therapy significantly improved sleep quality, reduced daytime sleepiness, and increased sleep duration and REM sleep in patients with minimal HE (31, 33). Sedative and hypnotic agents like zolpidem and hydroxyzine have been employed, though their benefits are tempered by potential side effects (31, 35, 39). Modafinil has improved daytime sleepiness in patients with primary biliary cirrhosis and OSA. Melatonin, often deficient in metabolism in cirrhosis patients, has proven effective at a dosage of 3 mg in improving sleep quality and diminishing daytime sleepiness (31, 33, 35). Furthermore, daridorexant, a dual orexin receptor antagonist, has shown promise in extending total sleep duration and reducing daytime

sleepiness in cirrhosis patients, though caution is advised for those with advanced cirrhosis (Child C class) (31). Trazodone proves efficacious for insomnia due to its elevated propensity for inducing somnolence compared to second-generation antidepressants, such as mirtazapine (42% versus 25%). It should be contemplated as a primary therapeutic option when insomnia constitutes a significant aspect of somatic symptoms, with mirtazapine serving as a viable alternative. Nonetheless, mirtazapine must be avoided in those with metabolic syndrome and obesity due to strong association with weight gain (approximately 3 kg after 8 weeks use). The undesirable effects associated with tricyclic antidepressants and monoamine oxidase inhibitors constrain their regular application in those with cirrhosis (34).

Continuous positive airway pressure is the treatment of choice for OSA, improving sleepiness and potentially benefiting liver health. Recent findings indicate that rifaximin significantly enhances objective sleep architecture, notably increasing REM sleep, after a 28-day treatment course as evidenced by 24-h polysomnography, although it did not alter subjective perceptions of sleep quality and sleepiness (31, 33). Another intriguing research avenue explored the synergy between the ammonia-lowering agent L-ornithine-L-aspartate (LOLA) and the vigilance-enhancing effects of caffeine. The results revealed that administering LOLA and caffeine effectively controlled the rise in capillary ammonia levels in healthy volunteers. Furthermore, caffeine decreased subjective sleepiness and influenced EEG amplitude across various brain regions, suggesting that this combination deserves deeper exploration in the context of caffeine administration timing in cirrhosis (34, 36). Behavioral therapies advocate for a consistent sleep–wake schedule, morning exposure to bright light, and cognitive behavioral therapy for insomnia, albeit the latter which is seldom available for cirrhosis patients. Additionally, mindfulness-based stress reduction, use of lavender baths and resveratrol, and supportive group therapy even though yielded minimal improvements in sleep quality, have not been conclusively recommended (31, 33, 36). A summary of sleep disorders, their mechanisms and management are shown in Figure 6.

7 Mental health disorders in cirrhosis

7.1 Prevalence and characteristics

Mental health disorders leading to poor quality of life and emotional distress profoundly impact patients with cirrhosis, leading to increasing severity of symptoms related to liver disease, advanced histological abnormalities, increased mortality rates, and poor adherence to medical treatments (40). Anxiety afflicts 25–45% of chronic liver disease patients, while depression affects a staggering 29–72% (41). The prevalence of depression varies among liver disease diagnoses, with notably higher rates in patients with MASLD and chronic hepatitis C, whereas patients with hepatitis B exhibit depression rates comparable to the general population. Nonetheless, emerging research highlights a stark reality on the other side – the prevalence of liver disease among psychiatric disorders: chronic hepatitis B and C are significantly more common among psychiatric populations than the public. A recent meta-analysis reveals hepatitis B prevalence in severe mental illness ranged from 2.2% in South America to a striking 9.7% in Asia, while in hepatitis C it was from 3.0% in South America to an alarming 17.4% in North America. Cohort studies further underscore this disparity, showing that schizophrenia patients suffer from chronic liver disease at a rate of 7.0%, compared to 6.1% in the general population. In individuals with bipolar disorder, the prevalence of chronic liver disease was as high as 13.9%, which is 2.7 times higher than the general population. Moreover, the current and lifetime prevalence of hepatic illness in bipolar disorder stands at 17 and 21%, respectively (42). Anxiety disorders are rampant among cirrhosis patients, severely diminishing their quality of life. Depression is also rampant in MASLD patients, with 23.6% meeting depression criteria. Another study revealed that patients with MASLD face 3.8 times higher odds of lifetime depression compared to those without liver disease. A recent study showed that nearly 1 in 6 patients with cirrhosis have moderately severe to severe depression and nearly half have moderate–severe anxiety (43). A study investigated the relationship between hepatic diseases and psychiatric symptoms, focusing on the prevalence and impact of mental health disorders in hospitalized cirrhosis patients in the United States from 2002 to 2014 and found that 37% of cirrhosis patients had a mental illness diagnosis, with prevalence rising from 22.6% in 2002 to 54.1% in 2014. Common mental health disorders included a history of mental health issues (49.4%), mood disorders (22.9%), substance use disorders (14.4%), anxiety (9.6%), and schizophrenia (2.4%), with a slight male preponderance (44). Authors from the United States, found that the prevalence of depression in cirrhosis was significantly higher at 23.93% compared to 7.61% in the non-cirrhotic control group. Multivariate analysis revealed that patients with liver cirrhosis had more than twice the risk of developing depression (odds ratio = 2.172), concluding that cirrhosis was an independent risk factor for developing major depressive disorder (45). In another study, mental health diagnoses were prevalent among cirrhosis patients and significantly increased the risk of all-cause mortality: 54% for any mental health diagnosis, 11% for non-alcohol-use disorder (AUD)/substance-use disorder (SUD), and 44% for AUD/SUD. The authors found that regular outpatient mental health visits can mitigate this risk, decreasing all-cause mortality by 21% for AUD/SUD patients, 9% for non-AUD/SUD, and 3% for any mental health diagnosis (46).

There are multiple causal pathways linking mental health disorders and cirrhosis. Inflammation and gut microbiota play crucial roles in both psychological distress and liver disease initiation and progression, while the "sickness behavior theory" explains that peripheral inflammation can lead to behaviors like fatigue, lethargy, impaired concentration, and social withdrawal. If these illness-associated behaviors persist, they can lead to the development of psychological distress, such as clinical depression and anxiety.

7.2 Assessment and management

Different scales and instruments, such as the hospital anxiety and depression scale and the generalized anxiety disorder score-7 and the patient health questionnaire-9 help measure anxiety and depressive symptoms in cirrhosis. In contrast, tools like the structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) can distinguish clinical diagnoses such as major depressive disorder or generalized anxiety disorder.

Depression ranges from everyday situational depression to major depressive disorder, characterized by profound hopelessness, helplessness, and biological symptoms such as sleep disorders and anhedonia and can be mimicked by symptoms of cirrhosis like

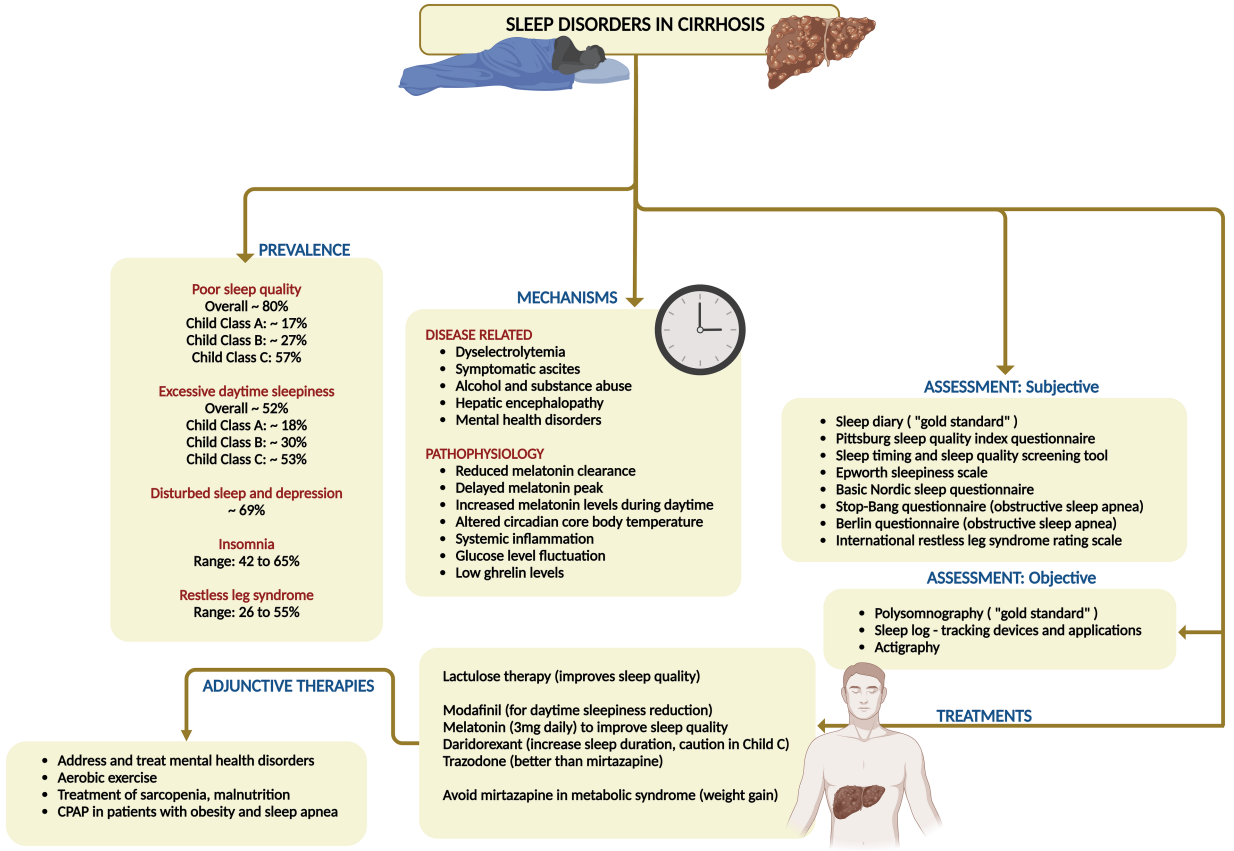

FIGURE 6
Summary of prevalence, mechanisms, clinical features, assessment, and management of sleep disorders in cirrhosis. CPAP, continuous positive airway pressure.

HE and delirium, necessitating careful psychiatric differential diagnoses. The key to treatment of mental health disorders such as depression and anxiety is to initiate patients on the lowest doses possible and titrate upward every 2 weeks depending on underlying liver disease severity, patient tolerance, and emergence of adverse events. Nonetheless, the recommended target maintenance dose for most medications in these categories for cirrhosis patients should be half standard dosing. For severe major depressive disorder [identified using a Patient Health Questionnaire (PHQ)-9 score $\geq$ 20], an integrated approach combining pharmacotherapy and psychotherapy is preferred. In contrast, mild-to-moderate major depressive disorder (PHQ-9 < 20) can be effectively managed with either second-generation antidepressants such as selective serotonin reuptake inhibitors (SSRI) or serotonin and norepinephrine reuptake inhibitors (SNRI) or psychotherapy alone. Second-generation antidepressants are favored for their proven efficacy and safety, with drug selection meticulously tailored to the patient's specific symptoms, side effects, comorbidities, and personal preferences. The landmark STAR*D study, which included a broadly representative "real-world" patient sample with both medical and psychiatric comorbidities, reported a 37% remission rate with citalopram as the first-line therapy (47). Despite second-generation antidepressants' low hepatotoxicity risk, caution is warranted when co-administered with non-steroidal anti-inflammatory drugs (due to serotonin transporter inhibition on platelets affecting platelet aggregation) and antiplatelets due to potential bleeding risks. Antidepressants should be commenced at low doses, with maintenance doses for SSRIs/SNRIs set at approximately half the standard dosing for cirrhosis patients to ensure a judicious balance between therapeutic efficacy and adverse effects. Cognitive behavioral therapy and interpersonal psychotherapy stand as the foremost behavioral therapies for depression, backed by robust evidence of their efficacy. The effectiveness of these treatments' hinges significantly on the patient's commitment to participate actively. Furthermore, additional therapeutic avenues, including family therapy, problem-solving therapy, relaxation techniques, and exercise programs, can be implemented, customized to the patient's tolerance and the severity of their condition (42, 48).

Anxiety in patients with cirrhosis poses a significant diagnostic challenge due to overlapping symptoms, necessitating meticulous differential diagnosis to prevent mismanagement. For mild generalized anxiety disorder (GAD; GAD-7score < 10) without functional impairment, regular follow-up may be adequate. However, for more severe cases, first-line treatments include SSRIs/SNRIs and cognitive behavioral therapy, beginning with low doses and adjusting cautiously is mandated. Patients unresponsive to SSRIs/SNRIs may be treated with medications such as buspirone, pregabalin, or hydroxyzine, with careful monitoring for precipitation of HE. If effective, drugs for anxiety disorder must be continued for a maximum of 12 months. If benzodiazepines are deemed necessary for patients with cirrhosis short-acting options like lorazepam, which lack active metabolites,

should be preferred to minimize the risk of drug accumulation. Nevertheless, the potential for benzodiazepine dependence restricts their use. Furthermore, cirrhosis patients administered benzodiazepines for three or more days face a heightened risk of first-time HE, likely due to increased cerebral benzodiazepine receptor availability, especially in those with alcohol use disorder. Additionally, medications such as pregabalin, due to its gamma-amino butyric acid (GABA) receptor agonism, and hydroxyzine, due to its anticholinergic effects, can also elevate the risk of HE, necessitating vigilant monitoring of cirrhosis patients on these treatments (42, 48, 49).

In addition to standard treatment options, less common but increasingly popular medications like vortioxetine and bupropion can be considered for patients with cirrhosis, as they are presumed to be safe for the liver. Vortioxetine, an antidepressant also used for generalized anxiety disorder, falls under the serotonin modulator and stimulator category. It has been associated with a low incidence of minor serum aminotransferase elevations during treatment and has not been linked to clinically apparent acute liver injury. Similarly, bupropion, an aminoketone antidepressant used for depression and smoking cessation, is rarely associated with clinically apparent liver injury (50, 51). Holistic management approaches, including aerobic exercise, mindfulness-based stress reduction, and yoga, are valuable adjunctive therapies, but require further validation for long term compliance and efficacy (42, 48). A summary of management of common mental health disorders in cirrhosis is outlined in Figure 7.

8 Gastrointestinal symptoms in cirrhosis

8.1 Prevalence and characteristics

Gastrointestinal symptoms worsen quality of life and impact daily routine in the lives of those with cirrhosis with approximately 80% of cirrhotic patients enduring these symptoms. These include abdominal bloating (49.5%), abdominal pain (24%), belching (18.7%), diarrhea (13.3%), and constipation (8%) according to various studies (52). Functional gastrointestinal disorders are common symptom complexes characterized by persistent and recurring gastrointestinal symptoms where no structural or organic pathology is identified and is commonly encountered in cirrhosis population. The intensity of these ailments mirrors the progression of liver disease, lactulose usage, severity and presence of ascites, mental health disorders, sleep abnormalities and psychological distress, as well as diminished serum testosterone levels. Studies have shown that the physical component of QoL assessment revealed a negative correlation with Child-Pugh scores. In cirrhosis, both physical and mental QoL significantly deteriorated with an increasing number of gastrointestinal symptoms. Furthermore, the prevalence of gastrointestinal symptoms was strongly linked to heightened anxiety, depression, and neuroticism scores (53).

The gastrointestinal symptoms are closely associated with a combination of factors, including motility disturbances, visceral hypersensitivity, altered mucosal and immune functions, changes in gut microbiota, and altered central nervous system processing which are highly prevalent in cirrhosis. Patients with cirrhosis frequently contend with premature satiety, curtailing their food intake, resulting in weight loss and related worsening of gastrointestinal symptoms (54). Compared to their healthy peers, cirrhotic patients harbor elevated plasma gastrin levels and a higher prevalence of peptic ulcers, often silent and intertwined with decompensated cirrhosis. *Helicobacter pylori* infections are more prevalent among cirrhotics with peptic ulcers, yet alcohol consumption and portal hypertension also play significant roles. The prevalence of peptic ulcer bleeding and re-bleeding are higher among those with cirrhosis, even though their prognosis during such episodes aligns closely with that of non-cirrhotic individuals (52, 54, 55). Furthermore, gastric sensorimotor function is impaired in those with cirrhosis. The presence of tense ascites disrupts gastric accommodation, while both gastric emptying and small bowel transit are slowed, likely due to imbalances in postprandial glucose, insulin, and ghrelin levels (55). These disturbances are also intertwined with insulin resistance in cirrhosis especially in those with metabolic syndrome. Additionally, delayed gut transit and small bowel manometry anomalies may pave the way for the rise of small bowel bacterial overgrowth and microbiome related changes and associated gastrointestinal dysfunction and related symptoms. Patients with cirrhosis have more obvious gastrointestinal symptoms and higher gastrointestinal hormone levels, which were closely correlated with the progression of liver cirrhosis and the degree of liver function damage (55, 56).

8.2 Assessment and management

Gastrointestinal symptoms in cirrhosis can be diagnosed to be secondary to functional causes and should follow the ROME IV criteria for classification and diagnosis. These diagnoses commonly include esophageal disorders (functional heartburn, reflux hypersensitivity, functional dysphagia), gastroduodenal disorders (functional dyspepsia, and nausea and vomiting disorders), bowel disorders (irritable bowel syndrome related constipation, diarrhea or mixed type, functional constipation or diarrhea and bloating/distension), centrally mediated abdominal pain syndrome, functional gallbladder disorder and anorectal disorders (57). It is imperative for the physician to assess the patient with cirrhosis thoroughly to rule out modifiable causes for these symptoms, before targeting treatment of psychosomatic and "functional" aspects of these symptoms. The modifiable causes for amelioration of gastrointestinal symptoms in patients with cirrhosis include: management of ascites, screening for and treating infections, correction of dyselectrolytemia (hyponatremia is a common cause of nausea and bloating in cirrhosis) including hypomagnesemia, drug treatment modification (titration of lactulose or switching to polyethylene glycol for better tolerance and management of HE), reassessing diet and medication history and identifying and stopping offending agents [over the counter use of pain medications causing abdominal pain, medications that promote nausea and vomiting (ursodeoxycholic acid, non-absorbable disaccharides), diarrhea (non-absorbable disaccharides, branched-chain amino acids) or constipation (curbing very high protein diet, over the counter supplements)], control of metabolic syndrome and screening for and managing cardiovascular and pulmonary disorders associated with cirrhosis or etiology of cirrhosis. It is also important for cirrhosis patients to follow a timed, frequent, well-spaced meal plan to improve satiety, target nutritional requirements and prevent gastrointestinal symptoms such as heartburn, reflux, bloating and dyspepsia. The large burden of gastrointestinal symptoms in cirrhosis can be adequately addressed by lifestyle changes and modification in medications. In the event of functional causes for the symptoms, then psychotherapeutic and pharmaceutical treatments to address the risks

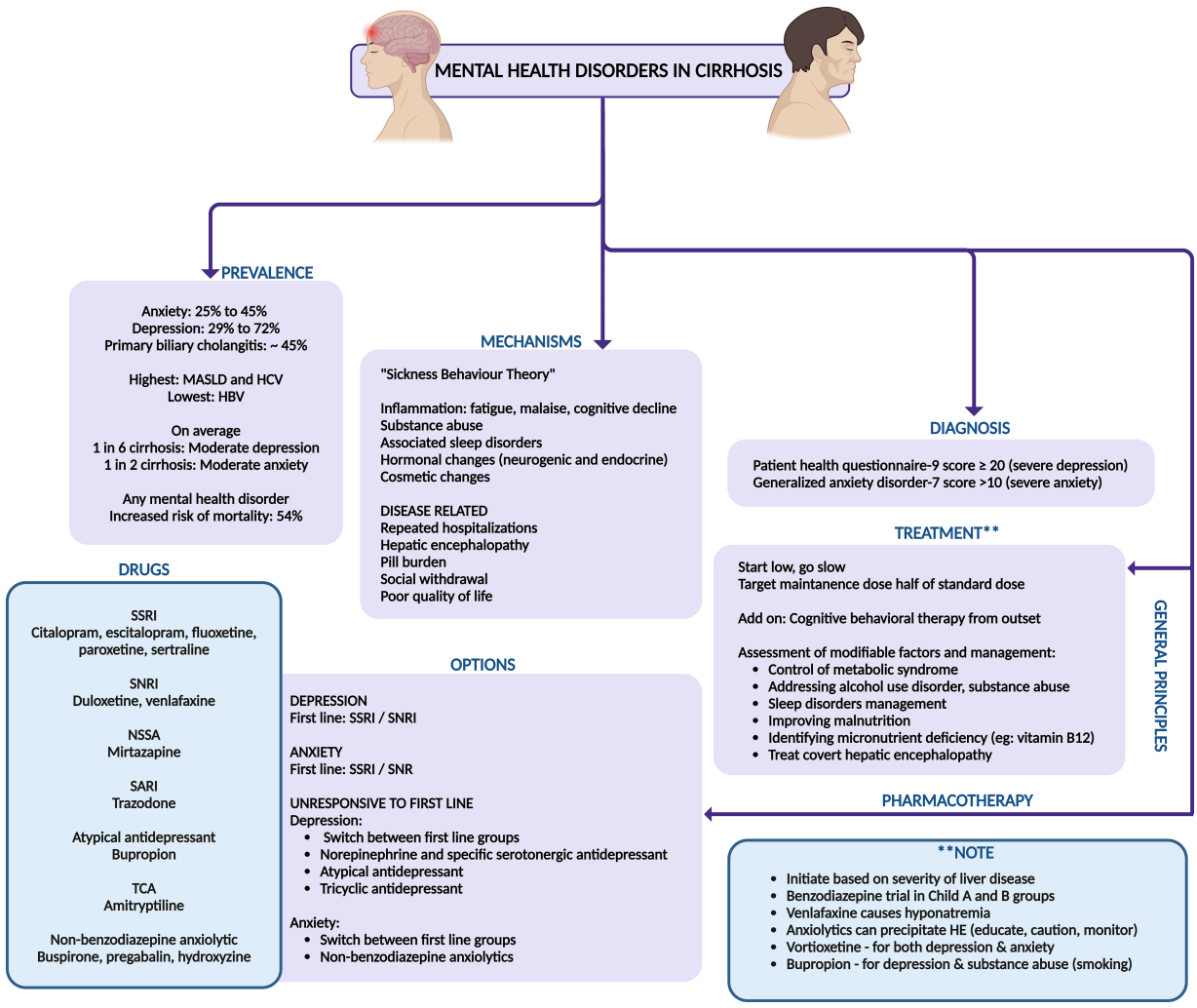

FIGURE 7
Summary of prevalence, mechanisms, diagnosis, and management of mental health disorders in cirrhosis. SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; NSSA, noradrenergic and specific serotonergic antidepressant; SARI, serotonin antagonist and reuptake inhibitor; TCA, tricyclic antidepressants; MASLD, metabolic-syndrome (dysfunction) associated steatotic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus.

(sleep abnormalities) and triggers (illness anxiety and other mental health disorders) may be initiated.

Contemporary research illuminates the efficacy of interventions like cognitive behavioral therapy (CBT) and biofeedback-assisted relaxation training (BART) (58). These therapies endeavor to reshape thought patterns and behaviors while bolstering self-efficacy, thereby enhancing overall health outcomes. Cognitive behavioral therapy, anchored in the principle that cognition molds emotions and actions, suggests that transforming thought processes can beneficially influence physical experiences. Negative thought patterns are often linked to adverse physical sensations, such as abdominal pain and discomfort. By retraining these thought processes, CBT can mitigate symptoms and elevate the quality of life (59). Biofeedback-assisted relaxation training therapies concentrate on observing physiological changes associated with thoughts and emotions, teaching patients to visualize the effects of their interventions. This intervention improves mood and somatic responses to anxiety disorders, thus alleviating the psychological and physiological distress that exacerbates gastrointestinal symptoms (60). Nonetheless, the short- and long-term benefits of these modalities in cirrhosis population remain an unmet need.

Pharmaceutical treatments, particularly antidepressants, have been meticulously studied for their efficacy in treating functional gastrointestinal symptoms. Tricyclic antidepressants like amitriptyline, selective serotonin reuptake inhibitors (SSRIs), and selective norepinephrine reuptake inhibitors (SNRIs) exhibit significant promise in symptom alleviation. Tricyclic antidepressants and SNRIs are notably effective in managing pain and enhancing quality of life, while SSRIs, though less potent for pain, can reduce anxiety and depression, indirectly soothing gastrointestinal symptoms (58–60). However, as previously discussed, these medications warrant well-designed clinical trials, and, cautious patient-centric use, weighing in factors such as metabolic syndrome, drug interactions, alcohol and substance use disorders, and the severity of liver disease and its complications (Figure 8).

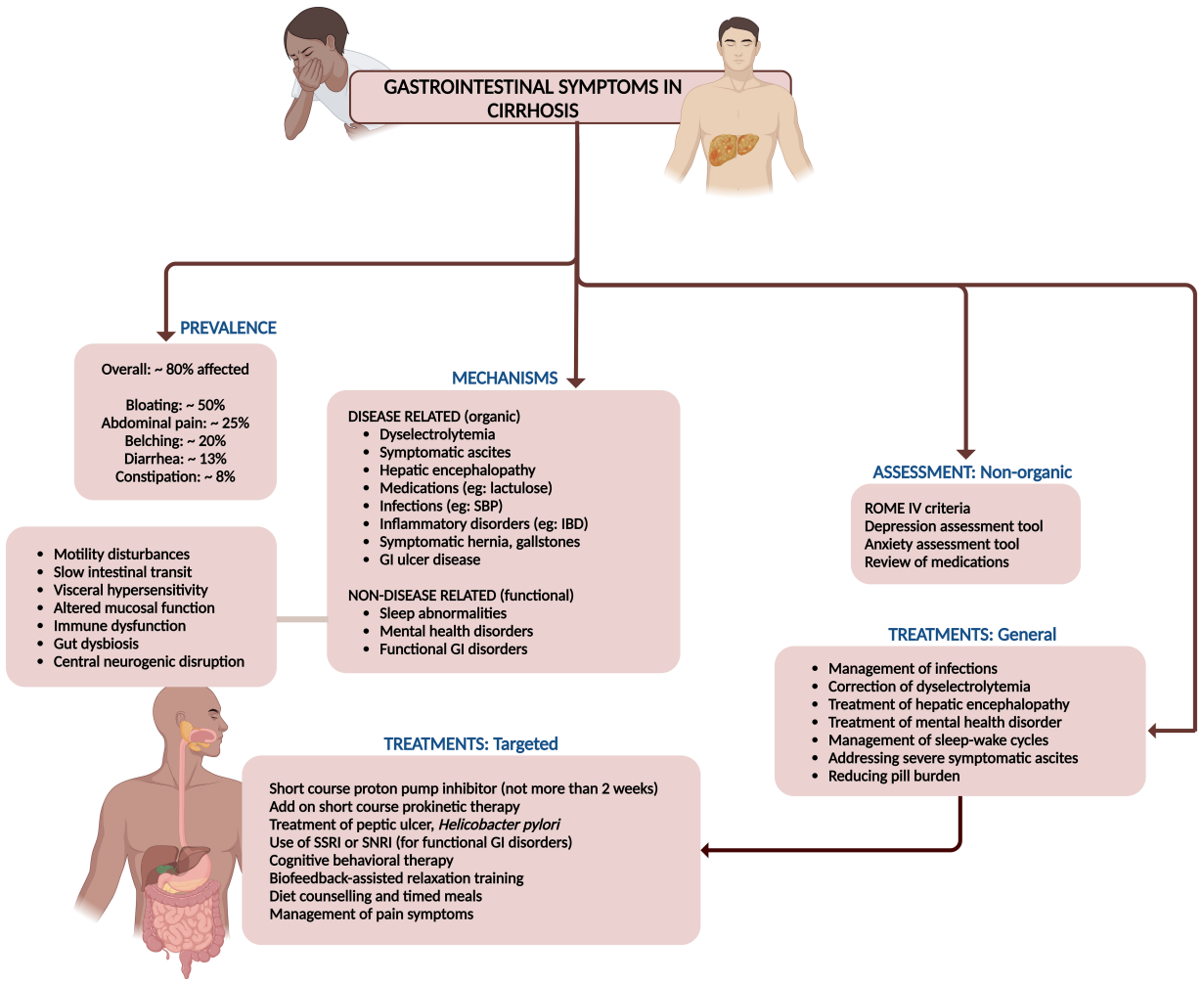

FIGURE 8
Summary of prevalence, mechanisms, assessment, and management of gastrointestinal symptoms in cirrhosis.

9 Sexual dysfunction in cirrhosis

9.1 Prevalence, types, risk factors and pathogenesis

Sexual dysfunction (SD) associated with liver diseases and cirrhosis is prevalent in a markedly high proportion of both men and women, yet it is frequently overlooked, underestimated, and ignored. Sexual dysfunction in men can present as low libido and erectile dysfunction (ED), while in women it can manifest as low libido, inability to achieve orgasm, painful intercourse (dyspareunia), as well as various menstrual irregularities such as anovulation, amenorrhea, oligomenorrhea, and dysmenorrhea (61).

For cirrhosis in general, the prevalence of ED was 70.3%, with a positive correlation between ED severity and increasing Child-Pugh (CTP) scores. In chronic viral liver diseases, the prevalence of ED was reported at 60% for individuals under 50 years and 88% for those over 50. Hepatitis B-related liver disease showed a total ED prevalence of 24.6%, with higher rates in HBV-related liver cirrhosis (41.2%). For hepatitis C, the reported prevalence was 30% among patients aged 20–80 years. In alcohol-related liver disease, the prevalence was found to be 61% in men under 56 years. Lastly, chronic liver disease in general, with a mean age of 54.8 years, showed a 50.6% prevalence of ED. Among women cirrhosis on the liver transplant wait list, reportedly, 42% had irregular menstrual cycles, 28% irregular and unpredictable bleeding, and 30% amenorrhea (62).

Men with cirrhosis often exhibit hypogonadism and signs of feminization, including testicular atrophy, low testosterone levels, diminished libido, infertility, reduced secondary sexual hair, and gynecomastia. These symptoms are linked to reduced spermatogenesis and peritubular fibrosis in 50% of cases. In women with cirrhosis, chronic anovulation is prevalent, manifesting as secondary amenorrhea, oligomenorrhea, or irregular episodes of metrorrhagia. Amenorrhea is particularly common in women with both alcohol-related and non-alcohol-related chronic liver disease, and levels of testosterone, oestradiol, prolactin, and luteinizing hormone often differ significantly from those in healthy individuals (63).

The pathogenesis of SD is complex and can result from alterations of the hypothalamic–pituitary–gonadal (HPG) axis due to changes in sex hormone metabolism and encompass a range of physiological and psychological factors. Drug interactions, particularly with nonselective beta-blockers and diuretics like spironolactone, also contribute to SD. Additionally, the direct toxic effects of alcohol and its metabolite acetaldehyde, on the gonads are significant contributors (64). Metabolic

syndrome, including diabetes, hypertension, and autonomic neuropathy, plays a role, as does primary testicular dysfunction resulting from hypoestrogenism due to blood shunting in portal hypertension and associated with portosystemic shunt placement. Advanced age, physical changes, sarcopenia, and malnutrition are also implicated causes for SD in cirrhosis among both genders. Furthermore, advanced liver disease itself, characterized by higher liver disease severity scores, high hepatic venous pressure gradient, low serum albumin, and large-volume ascites and presence of neuropsychiatric manifestations of HE significantly impacts sexual function. Lastly, psychological factors like depression, anxiety, and stress, and sleep disorders, which can affect all phases of sexual function, are critical contributors to SD in cirrhosis (65). Additionally, in women with cirrhosis, menopausal symptoms can significantly contribute to sexual dysfunction due to the accompanying vasomotor, psychological, and physical changes. These changes encompass hot flushes, palpitations, insomnia, depression, bladder issues, and vaginal dryness. Consequently, these symptoms adversely impact sexual desire, libido, and arousal—three critical phases of normal female sexual function (66).

9.2 Assessment and treatments

For males, sexual dysfunction is measured using the International Index of Erectile Function (IIEF), which encompasses five domains: erectile function (EF), orgasmic function (OF), sexual desire (SD), intercourse satisfaction (IS), and overall satisfaction (OS). The severity of ED is categorized based on IIEF scores, with 5 or lower indicating no attempts at intercourse, 6–10 severe ED, 11–16 moderate ED, 17–25 mild ED, and 26–30 normal erectile function or no ED. Additional assessment methods for males include the Sexual Encounter Profile (SEP) diaries, Global Assessment Question (GAQ), and Quantitative Androgen Deficiency in Aging Males (ADAM) questionnaire (61, 62). For females, sexual dysfunction is assessed using the Female Sexual Function Index (FSFI), covering six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. An overall FSFI score below 26.55 is indicative of female SD, with scores ranging from 2 to 36. Other methods for assessing female sexual dysfunction include the Golombok Rust Inventory of Sexual Satisfaction, Brief Index of Sexual Functioning for Women, Changes in Sexual Functioning Questionnaire, Derogatis Interview for Sexual Functioning, and the FSFI, validated for use in liver diseases (61, 62).

In general, the evaluation of SD involves the adequate treatment of primary liver diseases, asking leading questions about sexual and psychological issues, and conducting a detailed targeted history along with a careful pelvic examination. Relevant investigations and the use of questionnaires for SD assessment are essential. Treatment of SD focuses on identifying and addressing the primary cause of the dysfunction. This includes providing counseling and psychological support, treating the underlying liver diseases, and offering supportive treatments specifically for SD. Evaluating SD in individuals with cirrhosis requires a thorough assessment, encompassing routine laboratory tests such as complete blood count, coagulation profile and biochemistry (including urea, electrolytes, and serum creatinine), alongside reproductive hormone levels (61–63).

In men, this evaluation entails measuring testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and sex hormone-binding globulin (SHBG). The initial step in diagnosing androgen deficiency is to measure total testosterone from a morning blood sample. If total testosterone is low or borderline and symptoms of reproductive dysfunction are evident, further analysis of free or bioavailable testosterone (including SHBG measurement) and concurrent LH and FSH values is warranted. Reference ranges for reproductive hormones vary with assay platforms, and free testosterone, calculated using Vermeulen's formula, provides a more precise evaluation of androgen status, particularly in cirrhosis where SHBG production is altered. In cases of hypogonadism, LH and FSH levels help differentiate between primary testicular dysfunction (elevated LH and FSH) and hypothalamic or pituitary insufficiency (low or normal LH and FSH) (61, 62).

For female patients, a detailed menstrual history is imperative, beginning with an evaluation of FSH, LH, prolactin, and thyroid-stimulating hormone. Elevated prolactin necessitates further investigation into hyperprolactinemia, while abnormal thyroid-stimulating hormone levels indicate thyroid dysfunction. Elevated LH and FSH suggest primary ovarian failure, whereas low or normal levels in the absence of regular menses point to potential hypothalamic or pituitary issues, although low-normal LH and FSH can also be observed in polycystic ovarian syndrome and during the normal menstrual cycle. Ideally, FSH and LH should be measured on the third day of the menstrual cycle. For suspected anovulation, measuring serum progesterone within the luteal phase can indicate ovulation if the levels fall within the luteal reference range or exceed 5 ng/mL, though levels below the expected range do not exclude ovulation, particularly if the sample is collected outside day 21, which is common in women with irregular menses (61, 62).

For both genders, the approach emphasizes adequate treatment of primary liver diseases, joint counseling for both partners, environmental modifications to ensure a suitable place and timing for sexual activity, and the avoidance of supplements, including complementary and alternative medicine, and over-the-counter medicines that are not evidence-based. For males, treatment options for ED include the use of phosphodiesterase-5 (PDE5) inhibitors, with caution in Child-Pugh class C patients. Specific medications listed include sildenafil (starting dose 25 mg), tadalafil (dose 10 mg, with longer half-life and better compliance), vardenafil (dose 5 mg, maximum 10 mg), and avanafil, which is a newer agent with limited experience. For females, the treatment strategy covers various aspects of sexual dysfunction. Anovulation and amenorrhea can be managed with oral contraceptive pills or estrogen therapy. Hormone replacement therapy is suggested for menopause. Reduced libido should be treated by identifying and addressing depression and providing psychosocial support. Reduced arousal can be managed with lubricants and inability to orgasm may be aided by clitoral stimulation devices and sex aids. Additionally, lifestyle modifications are advised, such as pelvic floor exercises for women depending on the stage of cirrhosis, and cessation of smoking and alcohol consumption for both genders. To address anemia-related performance issues in sexual activity, blood transfusions or intravenous iron therapy may be necessary. Forced sexual acts may increase the risk of bleeding and must be cautioned against. Strategies to enhance arousal include couples counseling, sex education with videos and literature, education on sexual positions, creating a conducive environment for sexual pleasure, and extending foreplay time. Cognitive behavioral therapy can also help by removing sexual inhibitions and enhancing

sexual involvement by positively targeting interpersonal relationships (Figure 9) (61–63, 65).

10 Pain and peripheral neurological symptoms

10.1 Prevalence and clinical characteristics

Recurrent or chronic pain is a prevalent symptom among individuals with cirrhosis, frequently necessitating the prescription of analgesic medications. A systematic review encompassing five studies revealed that the prevalence of pain in patients with end-stage liver disease varied between 30 and 79% (3). Moreover, a database study from the Veterans Health Administration, indicated a temporal increase in the annual percentage of patients receiving opioid prescriptions, rising from 36% in 2005 to 47% in 2014 and mental health disorders and hepatic decompensation were independently associated with long-term opioid prescriptions (66). Reporting of pain in at least one region was notable in 75.6% patients in a study and chronic pain and wide spreading pain were associated with mood and cognitive disturbance, fatigue, sleep difficulty, and physical and social functioning in patients with cirrhosis (67). Chronic pain is reported by 40–79% of patients with cirrhosis and a pertinent influence on poor functional status and quality of life (68).

There are different phenotypes of pain symptom in cirrhosis which has their own pathophysiology and treatment options and responses. Pain is classified acute (≤3 months) or chronic types (>3 months) and into nociceptive, neuropathic, and nociplastic categories, each demarcated by distinctive mechanisms, clinical manifestations, diagnostic protocols, and therapeutic interventions.

Nociplastic pain, stemming from altered nociception without evident tissue damage, manifests as pervasive, fluctuating pain with accompanying symptoms of sleep disturbances, psychological distress, cognitive impairments, and fatigue. Fibromyalgia serves as the quintessential example, also observed in patients with early or advanced cirrhosis. Patients typically report fluctuating, widespread dull or aching pain, which may also include neuropathic characteristics such as burning or tingling. They often experience concurrent issues like sleep disturbances, psychological distress, memory problems, fatigue, and heightened sensitivity to sensory stimuli like light or unpleasant smells. A patient's history may reveal a prolonged struggle with pain and associated symptoms that have been resistant to conventional analgesics or treatments targeting peripheral pain, such

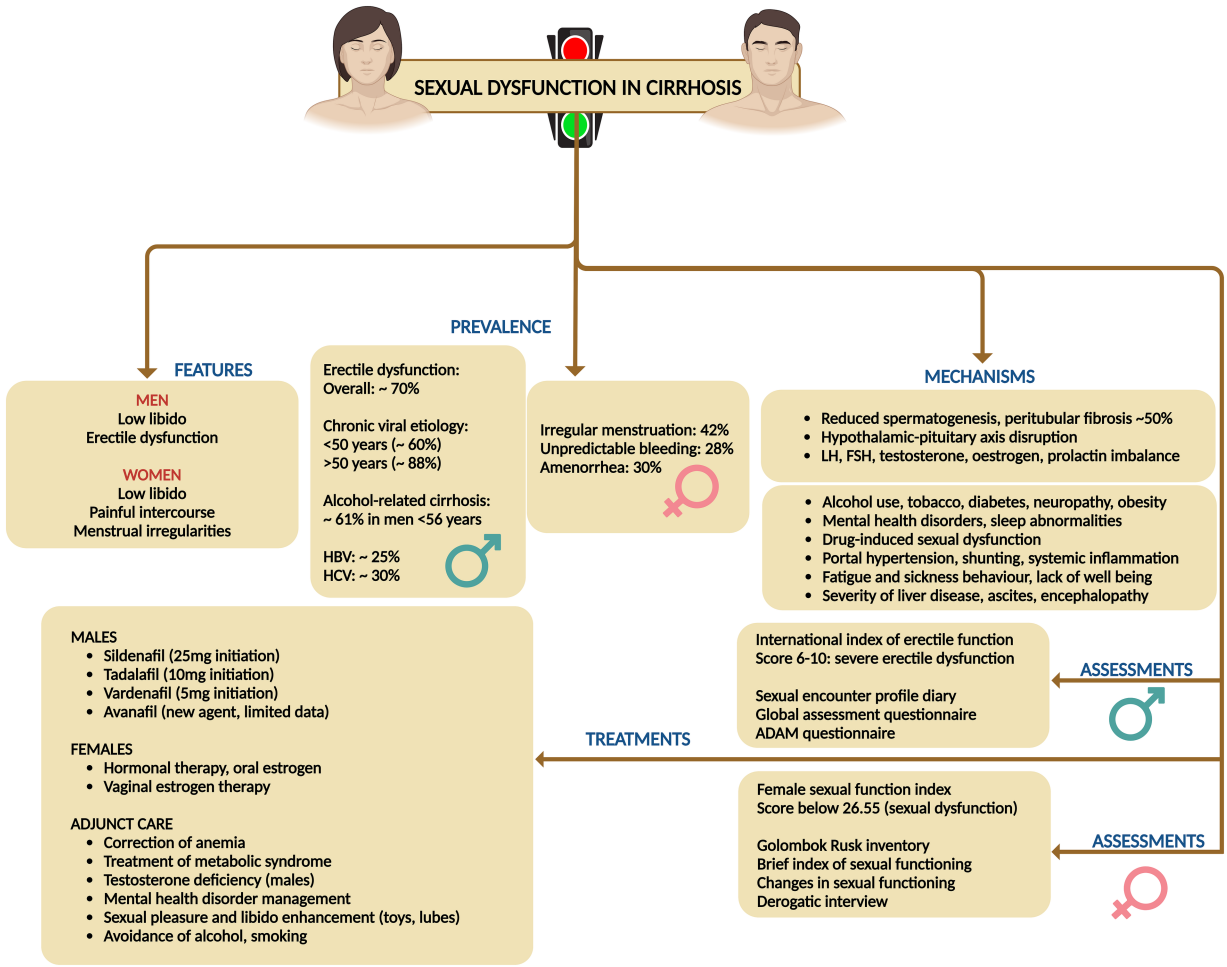

FIGURE 9
Summary of prevalence, mechanisms, assessment, and treatments related to sexual dysfunction disorders in cirrhosis.

as injections. Additional indicators of nociplastic pain include extensive healthcare utilization, high levels of pain-related distress, and a family history of chronic pain or psychological disorders. Psychiatric conditions, especially mood disorders, frequently coexist with nociplastic pain, suggesting a bidirectional relationship due to shared risk factors like trauma and common disease mechanisms involving neurotransmitters. The diagnosis is primarily clinical, although questionnaires can help evaluate pain location and severity. The 2016 Fibromyalgia Survey Criteria, a self-report tool, assesses pain distribution via the widespread pain index and symptom severity via the symptom severity scale, with the resulting Fibromyalgia Severity Score serving as a measure of central sensitization (69–72).

Nociceptive pain, arising from actual or imminent tissue injury, encompasses well-defined somatic pain or diffuse visceral discomfort accompanied by autonomic symptoms such as nausea and diaphoresis. This type of pain is diagnosed via meticulous physical examination and imaging studies. Examples include trauma and surgical interventions, and specifically in cirrhosis, conditions such as fractures, severe ascites, discomfort of splenomegaly, muscle cramps, musculoskeletal disorders-related pain, and tender gynecomastia induced by aldosterone antagonists. Somatic nociceptive pain is typically well-localized, reproducible, and proportional to the causative injury, while visceral nociceptive pain tends to be diffuse, with referred pain to superficial regions and often accompanied by autonomic symptoms such as sweating, changes in heart rate, and nausea. Pain descriptors with high specificity for nociceptive pain include terms like "heavy, stinging, lacerating, and suffocating." Although diagnosing nociceptive pain can be complex due to the potential presence of mixed pain components—nociceptive, neuropathic, and nociplastic—a definitive physical examination or diagnostic testing, such as imaging, can often identify a treatable source of pain (73–75).

Neuropathic pain, precipitated by lesions or pathologies of the somatosensory system, is characterized by aberrant sensations following neuroanatomical pathways, diagnosed through comprehensive physical evaluations, confirmatory testing, and instruments like the Neuropathic Pain Questionnaire and painDETECT screening tool. This pain, characterized by originating from regions with abnormal sensation, may present as pain in the absence of stimuli, pain from normally nonpainful stimuli (allodynia), or disproportionate pain in response to harmful stimuli (hyperalgesia). The pain can range from tingling and numbness to sharp, stabbing sensations and may exhibit temperature variations such as burning or cold. Neuropathic pain typically adheres to a neuroanatomical distribution. Should a patient display neuropathic pain, particularly allodynia in a glove and stocking distribution, alongside dysautonomia symptoms like orthostatic hypotension or micturition disorders, small fiber neuropathy should be suspected (76–79).

Cirrhosis presents formidable challenges in the realm of pain management due to the absence of a consensus on treatment protocols and the constrained pharmacologic arsenal. Recommendations advocate for a restrained use of acetaminophen (≤2 g per day) and avoidance of NSAIDs and opioids. The peril associated with any pharmacologic intervention in cirrhotic patients is considerable, given the propensity of NSAIDs to exacerbate ascites, renal impairment, and gastrointestinal hemorrhage. Even a brief NSAID regimen can significantly impair renal function, diminish the effectiveness of diuretics like furosemide, and disrupt hemostasis through inhibited platelet aggregation and thromboxane B2 synthesis. Opioids are frequently co-prescribed with benzodiazepines, compounding the risk of adverse outcomes, including falls and potential overdose fatalities. Thus, a judicious selection of pain management strategies is crucial to ameliorate pain control while mitigating severe complications (67, 68, 80).

10.2 Mechanisms and epidemiology

Nociplastic pain stems from central sensitization, involving abnormal pain processing in the peripheral and central nervous systems, leading to increased sensitivity and reduced inhibition. Quantitative sensory testing reveals heightened temporal summation and diminished conditioned pain modulation in chronic pain conditions, indicating supraspinal mechanisms. Imaging studies show structural and functional CNS alterations, highlighting CNS dysfunction as a key pain driver. Recognizing nociplastic pain is vital in cirrhosis, where analgesic decisions are complex. Research indicates that 27% of cirrhosis patients exhibit fibromyalgia symptoms, a quintessential nociplastic pain condition, often accompanied by mood and sleep disturbances indicative of centralized pain states (67, 68). Cognitive impairments are also widespread, ranging from subtle executive function deficits to severe disorientation, with minimal hepatic encephalopathy present in up to 80% of cirrhosis patients. These findings suggest a substantial degree of central sensitization in cirrhosis, highlighting nociplastic pain as a crucial component of chronic pain in these patients (68, 81).

Nociceptive pain, the most comprehended form of pain, emerges from actual or potential tissue damage due to nociceptor activation within a normal sensory nervous system. While nociceptive pain can contribute to chronic pain, it predominantly presents as acute pain, subsiding once the injury heals and inflammation diminishes. In cirrhotic patients, nociceptive pain arises from various sources such as pathological fractures, ascites, splenomegaly, muscle cramps, musculoskeletal diseases like avascular necrosis and septic arthritis, and mastalgia (67, 68, 82).

Neuropathic pain, stemming from lesions or maladies afflicting the somatosensory nervous system, precipitates aberrant sensory processing within the brain and spinal cord. This encompasses a myriad of conditions, including diabetic neuropathy, painful polyneuropathy, painful radiculopathy, trigeminal neuralgia, and small fiber neuropathy. Peripheral neuropathy, frequently associated with neuropathic pain symptoms, is notably prevalent in cirrhosis, irrespective of diabetes or alcohol abuse. Although the precise prevalence of painful peripheral neuropathy in cirrhosis remains elusive, research has revealed that 15% of cirrhotic patients manifest neuropathic symptoms such as numbness and paraesthesia (67, 68).

10.3 Treatment and adjunctive management

General principles include addressing comorbid symptoms (such as sleep, mood, memory, fatigue, and psychiatric disorders), emphasizing self-management tools, and employing multimodal therapies that combine several non-pharmacologic strategies. Self-management domains cover emotions, cognitions, behaviors, sleep, and environment, with strategies like mindfulness, pleasant activities, social support, and behavioral sleep techniques (67, 68, 83).

For managing nociceptive pain, pharmacologic treatments include the administration of acetaminophen at a dosage of 500 mg every 6 h, with a maximum limit of 2 g per day. Topical NSAIDs like

diclofenac gel are recommended (due to very low systemic absorption). Opioids such as oxycodone, dosed at 2.5 mg as needed, and hydromorphone at 1 mg every 6 h as needed should only be used for acute pain that is severe or unresponsive to initial therapies not for more than 3 days. It is crucial to ensure an effective bowel regimen to counteract opioid-induced constipation. Interventional treatments for nociceptive pain may involve surgical interventions to address the peripheral pain source, as well as injections, nerve blocks, neurostimulation, and intra-articular injections (68, 80, 84).

In the case of neuropathic or nociplastic pain, pharmacologic options include the use of lidocaine patches and topical capsaicin. Tricyclic antidepressants, such as cyclobenzaprine are dosed at 5–20 mg or nortriptyline, initiated at a dose of 10 mg at bedtime, while SNRIs like duloxetine and venlafaxine are started at 30 mg and 37.5 mg daily, respectively, titrated to a maximum of 50% of that used in non-cirrhotic population. Tramadol is considered to have a more favorable side effect profile compared to other opioids. However, data supporting this are scarce in cases of cirrhosis. Additionally, tramadol can lower the seizure threshold and poses a risk of serotonin syndrome when taken with other medications (83). Gabapentinoids, including gabapentin starting at 300 mg daily and pregabalin at 50 mg twice daily, are also utilized. It is imperative to monitor patients for sedation and fall risks associated with these medications (68, 79, 85). Treatment of nociplastic pain must also include adjunct cognitive behavioral therapies or physical therapy alongside an approved therapist. Specific diet, alternative manual therapies such as acupressure and acupuncture that are based on pseudoscientific principles are not studied via well-designed trials or found beneficial for pain management in cirrhosis population are not recommended. These judicious approaches categorizing pain types aims to tailor management to the individual needs of cirrhotic patients, ensuring a comprehensive and multifaceted care plan that addresses both the physical and psychological aspects of chronic pain. A summary of pain management in cirrhosis is shown in Figure 10.

11 Hair loss and skin changes

11.1 Prevalence and clinical characteristics

Even though the actuarial prevalence of hair loss and its types, and major skin changes and its types related to symptom-burden in cirrhosis is not well documented or studied, generalized complaints of hair loss and skin changes are routine discussion inside the liver outpatient. Hair loss and significant skin changes increase consciousness and affect mood, emotions, and mental health of the patient with cirrhosis.

Alopecia refers to the absence or loss of hair in areas where hair is typically present and is a common symptom and sign in cirrhosis. This condition can be either localized or widespread, and may be temporary or permanent. It affects both men and women across all age groups. Alopecia is recognized as a symptom arising from a variety of causes and is broadly categorized into nonscarring (the most common type and most common notable in cirrhosis) and scarring (cicatricial) forms. The impact of alopecia can cause considerable emotional distress, significantly diminishing the quality of life for those affected (86, 87).

Hair loss, specifically the loss of pubic hair or beard, is linked to cirrhosis and is associated with elevated estrogen levels. Gynecomastia, characterized by breast enlargement, occurs in 44% of cirrhosis cases, also due to elevated estrogen levels, and is related to conditions like extreme obesity, hypogonadism, and various adrenal and testicular diseases (88, 89). Cirrhosis also leads to pigmentation changes, with 46.9% of patients experiencing blotchy or diffuse muddy gray hyperpigmentation. Leg ulcers in cirrhosis patients result from necrotic tissue due to hypoxia and venous reflux obstruction, with similar occurrences in chronic venous insufficiency and diabetes (89, 90). Lastly, coagulation defects in cirrhosis, manifesting as petechiae, ecchymoses, or mucosal bleeding, are due to thrombocytopenia and other hemostasis abnormalities, like those seen in hematologic disorders and anticoagulant therapy for thrombotic diseases. Dermatological vascular manifestations in cirrhosis include palmar erythema, characterized by blanchable redness in the thenar eminence and fingertips, is seen in 23% of cirrhosis cases due to changes in peripheral hemodynamics and increased estrogen levels, with similar conditions found in rheumatoid arthritis and diabetes. Spider angioma, involving central arterioles surrounded by radiating capillaries, occurs in 33% of alcohol-associated cirrhosis cases and is also linked to hepatopulmonary syndrome, arising from increased blood flow to the surface capillaries. Arteriovenous haemangiomas, presenting as bluish erythematous papules on the neck and chest, are associated with elevated estrogen levels in cirrhosis (91, 92).

11.2 Broad principles of evaluation and management

Female cirrhosis patients are most conscious about hair loss. The most common type of hair loss noted in cirrhosis population is telogen effluvium, a noninflammatory alopecia, impacts the entire scalp and can be triggered by stress, illness, pregnancy, malnutrition, infections, endocrine disorders, surgeries, and certain medications. Hair loss usually occurs 3 months post-trigger and resolves within 6 months. A positive hair-pull test conducted at various scalp locations indicates active shedding linked to telogen effluvium. Light microscopy examination of hair shafts can confirm these as telogen hairs. Dermoscopy can help differentiate chronic telogen effluvium, characterized by hair loss lasting over 6 months, from female-pattern hair loss, which shows greater variability in hair diameter. Additionally, the wash test or modified wash test can be useful in evaluating the severity of the condition (89, 93, 94). Telogen effluvium is reversible when an identifiable trigger is controlled. The hair shedding takes 3–6 months to cease and cosmetically significant regrowth may take 12–18 months. Additionally, correcting hypo-functioning thyroid, treating iron and zinc deficiency (and other documented macro and micronutrient deficiencies) also help ameliorate symptoms (94, 95).

Tamoxifen, an estrogen blocker, is effective in treating recent-onset and tender gynecomastia (after stopping or switching spironolactone) when administered at doses of 10–20 mg twice daily. Generally, up to 80% of patients experience partial to complete resolution of symptoms. It is generally used for 3 months before considering a surgical referral, the latter performed for cosmetic reasons and only in stable cirrhosis patients after weighing risk to benefit ratio (96, 97).

Symptomatic skin changes that are part of patient-related complaints mostly include localized or generalized hyperpigmentation and darkening over face or body parts. There are no recommended treatment options in this scenario unless an identifiable cause for the skin condition is present.

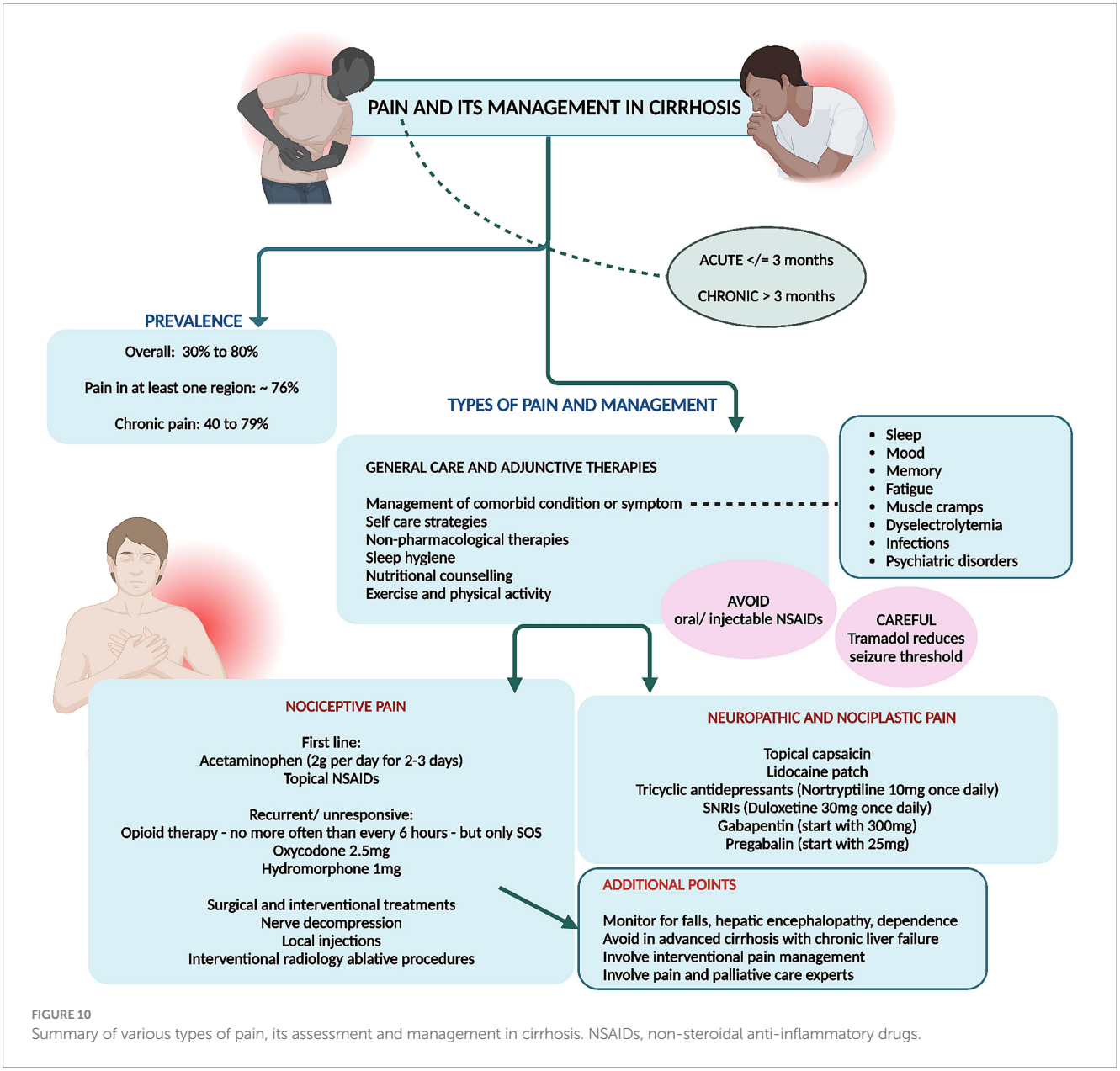

FIGURE 10
Summary of various types of pain, its assessment and management in cirrhosis. NSAIDs, non-steroidal anti-inflammatory drugs.

Skin lightening creams and intravenous or oral glutathione do not offer reasonable clinical benefit over placebo effect, are not associated with long term improvements, harbor potential adverse events (heavy metal toxicity and renal injury) or lack safety data (intravenous glutathione) and hence, not recommended (98–100).

12 Conclusion

This comprehensive review delves into the diverse array of symptoms and their management in patients with cirrhosis, underscoring the profound impact these symptoms have on quality of life. Commonly encountered symptoms include pain, muscle cramps, sleep disturbances, psychological symptoms, and gastrointestinal issues. Pain, prevalent in 30–79% of patients, often necessitates analgesics, with chronic pain linked to poor functional status. Muscle cramps, occurring in up to 68% of cirrhosis patients, are treated with medications like zinc, taurine, and branched-chain amino acids, although robust evidence for these treatments is lacking. Sleep disturbances affect up to 80% of cirrhosis patients, with insomnia and excessive daytime sleepiness being particularly prevalent. Management includes lactulose, melatonin, and behavioral therapies and mindfulness. Gastrointestinal symptoms are widespread, affecting 80% of patients, and include abdominal pain, bloating, and diarrhea. These symptoms are closely tied to the severity of liver disease and significantly diminish quality of life. Management strategies emphasize lifestyle modifications, dietary adjustments, and psychological support. Mental health disorders, including depression and anxiety, are common, exacerbating the burden of cirrhosis. Treatment involves a combination of pharmacotherapy and psychotherapy, tailored to individual patient needs. Sexual dysfunction, affecting both men and women, is often overlooked but significantly impacts quality of life.

Management includes addressing underlying causes, lifestyle changes, and counseling. Pruritus, a common and distressing symptom, is managed with moisturizers, antihistamines, and other medications like cholestyramine, though many treatments have limited efficacy. Hair loss and skin changes also contribute to the psychological burden of cirrhosis, necessitating a holistic approach to patient care. Overall, this review emphasize the need for comprehensive, multidisciplinary management strategies to address the complex symptomatology in cirrhosis, aiming to improve patient outcomes and quality of life.

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CP: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The author declares 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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Spleen stiffness measurements during recompensation in patients with acutely decompensated liver cirrhosis: preliminary findings of a pilot study

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Background: Acute decompensation (AD) in patients with liver cirrhosis is associated with a dramatic deterioration in prognosis. Immediate initiation of appropriate recompensation measures is essential to improve patient's outcome, although objective parameters for evaluating the success of recompensation are still lacking. Spleen stiffness measurements (SSM) have emerged as promising non-invasive tool to assess clinically significant portal hypertension (CSPH), which is the main driver of acute decompensation. However, while SSM accurately predicts CSPH and its complication, currently no data are available on its diagnostic performance during recompensation. This pilot-study aimed at evaluating changes in spleen stiffness following the initiation of recompensation measures in cirrhotic patients hospitalized due to AD.

Methods: In this prospective pilot-study, 60 patients with cirrhosis showing AD were included. Liver stiffness measurements (LSM) and SSM were performed on admission and repetitive SSM on day 3 and 5, respectivele, during recompensation measures. A cohort of patients ($n = 10$) with compensated cirrhosis served as control.

Results: A total of 36 data sets from the originally enrolled 60 patients were eligible for final analysis. On admission, patients with AD revealed a significantly increased spleen stiffness compared to the control group (70.51 vs. 29.06 kPa, $p < 0.0001$). Following the initiation of recompensation measures SSM revealed a significant reduction in spleen stiffness compared to the baseline assessment on day 3 (−18.5 kPa, −21.53%; $p = 0.0002$) with no further decrease on day 5 (−17.63 kPa, −21.23%; $p = 0.0326$).

Conclusion: Repetitive SSM seems to be a useful non-invasive clinical marker to assess the effectiveness of recompensation measures in cirrhotic patients with AD.

KEYWORDS

spleen stiffness, SSM, portal hypertension, decompensation, decompensated cirrhosis, CSPH, recompensation

1 Introduction

Liver cirrhosis represents the final stage of chronic liver diseases, such as chronic viral hepatitis, alcohol abuse or metabolic-dysfunction associated steatotic liver disease (MASLD), and is associated with high morbidity and mortality (1–3). The clinical course of liver cirrhosis can be divided into a compensated and a decompensated stage. Compensated cirrhosis is clinically defined as a stable stage of the disease characterized by absent or only minor symptoms (4, 5). Decompensated cirrhosis is defined by the manifestation of clinical complications, such as jaundice, ascites, portal-hypertensive bleeding, hepatic encephalopathy, or infections (3, 5, 6). The transition into a decompensated disease stage occurs at a rate of 4–12% per year and is linked to a considerably increased risk of experiencing further decompensating events, hospitalization and death, thus indicating a prognostic watershed in the clinical course of the disease (7, 8). After the first decompensation, further decompensating events occur in up to 60% of patients and mortality increases significantly (9). The key to improve the prognosis of patients with a decompensated cirrhosis is the rapid and complete recompensation with the aim to prevent further episodes of decompensation.

Recompensation is characterized by a resolution of liver-related complications, such as ascites, hepatic encephalopathy, or portal hypertensive bleeding along with an improvement of liver function. While a rapid and efficient recompensation appears to be essential, data on the assessment of hepatic recompensation are limited. The therapeutic success of recompensating measures is based primarily on the judgment of the treating physician and symptom assessment, while non-invasive biomarkers to monitor the recompensation process are lacking.

One factor that significantly influences the occurrence of decompensation, but also recompensation, is the severity of the underlying portal hypertension (10). Portal hypertension develops due to structural and functional changes in the cirrhotic liver and is a key driver of disease progression with its inherent risk of decompensation in patients with cirrhosis (10–13). Numerous studies have shown that a reduction of clinically significant portal hypertension (CSPH), for example with non-selective beta-blocker treatment, translates into a decreased risk of a first decompensation and adverse liver-related events, including repeated episodes of decompensation and liver-related mortality (10, 14, 15).

Different modalities are currently available to identify patients with CSPH that is defined as a hepatic venous pressure gradient (HVPG) $\geq$ 10 mmHg. However, while measurement of the hepatic venous pressure gradient is the gold standard for assessing CSPH, it represents an invasive procedure that is only available in experienced centers. Therefore, non-invasive tests, based on transient elastography, have become increasingly important to determine the severity of CSPH and its prognostic implications, as well as to guide treatment decisions (16, 17). In addition to liver stiffness measurement (LSM), spleen stiffness measurement (SSM) is also being carried out more frequently for risk prediction of acute decompensation, as SSM can detect early changes in portal hemodynamics (18–20).

SSM is an easily applicable vibration-controlled transient elastography technique, that allows real-time bedside assessment of CSPH (20–22).

Recent studies have demonstrated that SSM provides a valuable non-invasive surrogate marker of CSPH and is thought to outperform LSM in risk prediction for clinical decompensation (23).

However, whether and to what extend repetitive SSM may be helpful in the clinical assessment of recompensation rens unclear. Therefore, the aim of the present pilot study was to investigate the feasibility of repetitive SSM and its clinical usefulness after initiation of recompensation measures in patients with cirrhosis hospitalized due to acute decompensation.

2 Materials and methods

2.1 Study population and study design

For this prospective single-center pilot study, we included consecutive patients with cirrhosis after hospitalization due to acute decompensation at a tertiary care hospital (Department of Gastroenterology and Hepatology, University Hospital of Cologne, Germany) between 01/23 and 06/24, and performed LSM and repetitive SSM during recompensation. Acute decompensation of cirrhosis was defined as the development of ascites (>grade 1), overt hepatic encephalopathy, bacterial infection, hepatorenal syndrome, portal-hypertensive bleeding or a hepatic hydrothorax leading to hospital admission. Recompensation was defined as resolution of ascites and hepatic encephalopathy, absence of variceal re-bleeding, improvement of renal function parameter on laboratory analysis and control of infection. For recompensation, paracentesis was performed for ascites accompanied by adjustment of diuretics, administration of lactulose was performed for hepatic encephalopathy, administration of albumin and terlipressin for hepatorenal syndrome and endoscopic ligation together with non-selective beta blocker treatment in the case of variceal hemorrhage.

A group of patients with stable compensated cirrhosis, without any clinical signs of an acute decompensation, served as control group.

All patients with portal or mesenteric vein thrombosis, myeloproliferative diseases, previous abdominal surgery, transjugular intrahepatic portosystemic shunt, as well as patients with post-hepatic portal hypertension due to Budd-Chiari syndrome or cirrhose cardiaque were excluded from the study. Additional exclusion criteria were the presence of non-cirrhotic portal hypertensive diseases (e.g., hepatosplenic schistosomiasis, porto-sinusoidal vascular disease) as well as presence of a hepatocellular carcinoma or other hepatic malignancies, as well as failure of vibration-controlled transient elastography examinations or a lack of informed consent.

The presented study was conducted in accordance with the Declaration of Helsinki 1964 and its further amendments. Written informed consent was obtained by all study participants.

2.2 Liver and spleen stiffness measurements

Measurements of liver and spleen stiffness were performed by vibration-controlled transient elastography using the FibroScan® 630 Expert device (Echosens, Paris, France) with a 50 Hz probe for the liver and a 100 Hz spleen-dedicated module coupled with an ultrasound localization system, respectively (23–26).

In detail, LSM and SSM were performed in overnight fasted patients in a supine position with the right and left arms, respectively, in maximum abduction and by placing the transducer in the intercostal spaces, as previously described (26). For the SSM, the 100 Hz probe was placed at an ultrasound-targeted localization, where the spleen parenchyma had been previously identified. Results were expressed in kPa and LSM and SSM values were considered reliable, if at least 10 successful measurements were obtained, with a success rate of at least 60%, and an interquartile range (IQR) to median ratio <30% (26, 27).

Within this pilot study, SSM were initially only performed during the short-term course of recompensation measures, after admission (day 1), at day three (day 3) and day five (day 5) after initiation of recompensation measures. LSM was also performed at admission, at day one. In order to compare the values of the acute decompensation group, both SSM and LSM were also performed in a control group of individuals with stable compensated cirrhosis. The patients in the control group were recruited from the outpatient liver center. Blood samples for laboratory analyses were collected under fasting conditions (Figure 1).

2.3 Statistical analysis

For baseline characteristics, continuous variables are presented as means and standard deviation (SD), while the categorical variables are presented as frequencies with percentages. To compare differences between two groups, Student's *t*-test was used for continuous variables, while the Chi^2-test was employed for categorical variables. Statistical analyses were carried out using GraphPad Prism, Version 10.2.3 (Boston, MA 02110, USA). A two-sided *p*-value 0.05 was considered as statistically significant.

3 Results

In total, 60 patients with liver cirrhosis admitted to the hospital due to acute decompensation were evaluated for eligibility. After checking the eligibility criteria, 24 patients were excluded for the following reasons: early discharge (n = 7), new diagnosis of malignancy (n = 3), withdrawal of initial consent and rejection of further measurements (n = 5), misclassification (n = 4), inability of spleen stiffness measurements due to anatomical (n = 1) or technical reasons (n = 4) (Figure 1).

Finally, 36 patients completed at least two or more measurements of spleen stiffness during recompensation. In detail, 15 of these 36 patients were measured at day 1, 3, and 5 and 21 patients were measured at day 1 and 3 (Figure 1).

The mean age of the patients with acute decompensation enrolled was 60.8 ± 9.9 years, with 52.8% (n = 19) of them being male. The primary causes of cirrhosis in the study cohort of patients with acute decompensation were alcohol-related liver disease (42.7%) followed by MASLD (22.2%). The mean age of the control group was 58.5 ± 3.7 years, while 40% were female and the most common cause of cirrhosis was MASLD (40%), followed by alcohol (30%) and viral (30%). The clinical events of decompensation included the development of ascites in 12 patients (33.3%), hepatic encephalopathy in eight patients (22.2%), bacterial infection in seven patients (19.4%), hepato-renal syndrome in four patients (11.1%), gastrointestinal

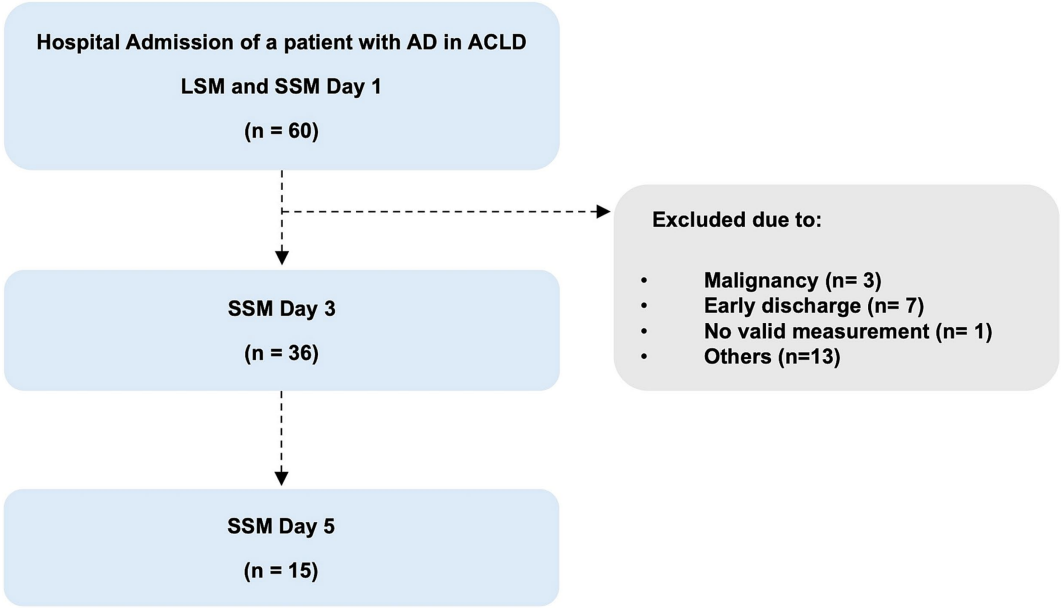


FIGURE 1
Flowchart of the study population. AD, acute decompensation; SSM, spleen stiffness measurement; LSM, liver stiffness measurement.

portal hypertensive hemorrhage in four cirrhotic patients (11.1%) and the manifestation of a hepatic hydrothorax in one patient with cirrhosis (2.8%). Of the four patients with portal hypertensive gastrointestinal bleeding, three patients already received NSBB (carvedilol) as a primary prophylaxis due to CSPH with high-risk varices or due to previous episodes of variceal hemorrhage. In one patient, NSBB treatment was newly initiated after the portal-hypertensive bleeding episode. In all patients, NSBB treatment was continued as secondary prophylaxis. Carvedilol was always used, and the treatment effectiveness was evaluated based on the change in heart rate.

On admission, the majority of decompensated patients presented with a Child-Pugh class B (52.8%), while 14 patients (38.9%) had a Child-Pugh class C and three patients with acute decompensation (8.3%) presented to the hospital with a Child-Pugh class A. All patients of the control group were in Child-Pugh class A.

At baseline, the mean Model for End-Stage Liver Disease (MELD) score of the study group was 16, compared to a mean value of nine in the control group ($p = 0.0011$). The mean baseline chronic liver failure consortium acute decompensation (CLIF-C AD) score was 53.9 ± 6.8, indicating an intermediate 3-month mortality risk (7, 28). After initiation of recompensation measures, the CLIF-C AD score reduced slightly to a mean value of 51.3 ± 6.9 on day 3 and to 51.05 ± 8.0 on day 5.

The baseline characteristics of the study population and the control group are shown in Table 1.

TABLE 1 Baseline characteristics.

Variable	Study cohort ($n = 36$)	Control group ($n = 10$)	p-value
Age, y	60.8 (9.9)	58.5 (3.7)	0.6364
Male:female, *n* (%)	19:17 (52.8%:47.2%)	6:4 (60%:40%)	–
BMI (mean)	25.6 (5.0)	29.6 (6.9)	0.0585
Etiology of liver disease, *n*			
Alcohol	17 (42.7%)	3 (30%)	–
Viral	4 (11.1%)	3 (30%)	–
MASLD	8 (22.2%)	4 (40%)	–
AIH/miscellaneous (PSC/PBC)	7 (19.4%)	0 (0%)	–
Child-Pugh class			–
A	3 (8.3%)	10 (100%)	–
B	19 (52.8%)	0 (0%)	–
C	14 (38.9%)	0 (0%)	–
INR	1.3	1.0	0.0006
Albumin (g/l)	29.5	42.0	0.0001
Bilirubin (mg/dl)	5.3	1.0	0.0851
Creatinine (mg/dl)	1.4	0.8	0.0398
Platelet count (x 10^3/ µl)	133.6	168.2	0.1937
AST (IU/L)	61.9	37.0	0.0440
ALT (IU/L)	32.5	31.0	0.8540
MELD	15.9 (6.0)	8.8 (4.3)	0.0011
CLIF C AD score			
Baseline	53.9 (6.8)		
Day 3	51.3 (6.9)		
Day 5	51.05 (8.0)		
Esophageal varices (y/*n*)	31/5	3/7	–
small	11 (30.6%)	2 (20%)	–
medium	20 (55.6%)	1 (10%)	–
large	0 (0%)	0 (0%)	–
Decompensating event			
Gastrointestinal bleeding	4 (11.1%)	–	–
Hepatic encephalopathy	8 (22.2%)	–	–
Bacterial infection	7 (19.4%)	–	–
Ascites	12 (33.3%)	–	–
Hepatorenal syndrome	4 (11.1%)	–	–
Hepatic hydrothorax	1 (2.8%)	–	–
LSM, kPa	55.7 (18.2)	23.53 (9.65)	<0.0001
Spleen size, cm	15.5 (2.5)	12.2 (3.4)	0.0016

Overview of the baseline characteristics of cirrhotic patients with acute decompensation and patients with compensated cirrhosis, serving as control group. Continuous variables are presented as means, standard deviation in brackets. Categorical variables are given as frequencies with percentages. BMI, body mass index; MASLD, metabolic-dysfunction associated steatotic liver disease; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis; INR, International Normalized Ratio; AST, aspartate aminotransferase; ALT, alanin aminotransferase; MELD, Model of End-stage Liver Disease.

3.1 Spleen and liver stiffness measurement

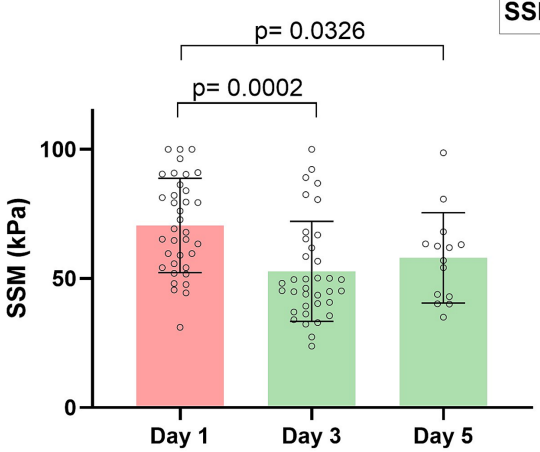
On admission (day 1), the mean spleen stiffness measured by transient elastography was 70.5 kPa ± 18.3 kPa, in patients with acute decompensation, compared to 29.1 kPa ± 11.2 kPa in the control group of patients with compensated cirrhosis ($p < 0.0001$). The mean longitudinal diameter of the spleen was 15.5 ± 2.5 cm in the group of patients with acute decompensation, compared to 12.2 ± 3.4 cm in the control group ($p = 0.0016$). The baseline liver stiffness (LS) was 55.7 kPa ± 18.2 kPa in the group of acute decompensated cirrhosis versus 23.5 ± 9.7 kPa in the control group ($p < 0.0001$).

After recompensation measures had been initiated, a significant reduction in spleen stiffness on day 3 of −18.5 kPa ($p = 0.0002$) was detected in the group of patients with acute decompensation. This corresponds to a relative decrease in spleen stiffness of −21.53% from day 1 to day 3 (Figures 2, 3).

On day 5 of recompensation, spleen stiffness continued to be significantly lower with a decline of −17.63 kPa ($p = 0.0326$), compared to the baseline measurement, corresponding to a relative spleen stiffness reduction of −21.23%. When comparing SSM values from day 3 and day 5, there was no further reduction, instead a plateau-effect (52.77 kPa vs. 57.99 kPa, $p = 0.4220$) could be observed (Figures 2, 3).

Among the 36 patients who received at least two sequential examinations, SSM remained stable in two patients, defined as a reduction of <10% in sequential SSM. Both patients were female and show ascites as decompensating event.

While the majority of patients with acute decompensation showed a reduction in SSM values on day 3 after initiation of recompensation, an increase in SSM on day 3 was observed in three patients indicating



	Day 1	Day 3	Day 5
SSM (kPa)	70.5	52.8	58.0

FIGURE 2
Spleen stiffness measurement (SSM) during recompensation measures. Parameters are given as mean in kPa. SSM, spleen stiffness measurement.

recompensation failure. Accordingly, the clinical evaluation of these patients also indicated that the initiated recompensation measures had not been successful. One patient showed weight gain due to rapid recurrent ascites after paracentesis, while another patient experienced acute esophageal variceal bleeding after the initial SSM had been performed. For the third patient, clinical recompensation could be achieved delayed, only at day 5.

In addition, after an initial decrease in spleen stiffness from day 1 to day 3, a renewed increase in spleen stiffness on day 5 was observed in six patients, while three patients showed only a mild increase of <20%. After initial recompensation, all of these patients developed clinical decompensation events such as renal failure (HRS) or recurrent ascites, after a short period of time, indicating that the recompensation measures were inefficient.

When considering the different etiologies patients with cirrhosis due to viral etiology showed the highest reduction (−32.48%) in SSM on day 3, followed by patients with MASLD (−28.64%), alcohol (−20.78%), and finally other etiologies like autoimmune hepatitis, primary sclerosing cholangitis or primary biliary cholangitis (−17.78%).

The control group with compensated cirrhosis showed a spleen stiffness of 29.1 ± 11.2 kPa on day 1 and 32.8 ± 8.6 kPa on day 3, respectively. Thus, there was no significant change between the SSM from day 1 to day 3 ($p = 0.41$) as could be expected in this stable clinical situation. Interestingly, spleen stiffness in patients of the control group was <45 kPa in every single measurement.

4 Discussion

The preliminary results of the present pilot study demonstrate that repetitive SSM may be a suitable clinical marker to assess the effectiveness of initiated recompensation measures in cirrhotic patients with acute decompensation.

SSM is an emerging tool in the armamentarium for diagnosing and monitoring patients with CSPH and predicting liver-related outcomes. Since objective measures are essential to standardize and optimize patient management, the use of SSM to assess the effectiveness of recompensation appears extremely useful (29).

To the best of our knowledge, this prospective study is the first analyzing the dynamic changes in spleen stiffness during recompensation in patients with acute decompensated liver cirrhosis.

In contrast to repeated LSM, which did not show a rapid adaptation to treatment measures in patients with acute decompensation (30), repetitive SSM can detect early changes in portal hemodynamics and provide relevant information regarding the effectiveness of initiated recompensation measures. In the present study, a significant reduction in spleen stiffness was observed only 3 days after the introduction of recompensation measures with a subsequent plateau effect. Therefore, in addition to a clinical evaluation, SSM could be a promising diagnostic tool to assess the immediate effectiveness of recompensation in everyday clinical practice. It is a high priority to evaluate the success of initiated recompensation measures timely, in order to identify any non-responders and to be able to adapt treatment concepts that has been initiated early on.

Unfortunately, the definition of "clinical improvement" and hepatic "recompensation" in patients with acutely decompensated liver cirrhosis is inconsistent. In 2021, the Baveno VII consensus conference introduced standardized criteria for the definition of hepatic recompensation, which requires cirrhotic patients achieving (i) a sustained cure with suppression or removal of the underlying etiology of cirrhosis, (ii) a resolution of complications such as ascites and hepatic encephalopathy after discontinuation of diuretic treatment and/or prophylactic therapies, as well as the absence of portal hypertensive bleeding for at least 12 month, and (iii) a stable improvement of liver function, assessed by liver function tests (e.g., serum albumin, bilirubin and INR) (22, 31). Though, a complete and long-lasting resolution of complications is difficult to achieve in clinical practice, since an irreversible alterations of liver structure typically goes along with a compromised liver function and repetitive decompensating events, making continuous treatment measures, e.g., with low dose diuretics, indispensable.

However, while the resolution of a hepatic decompensation following a successful treatment is inevitably linked to an improvement

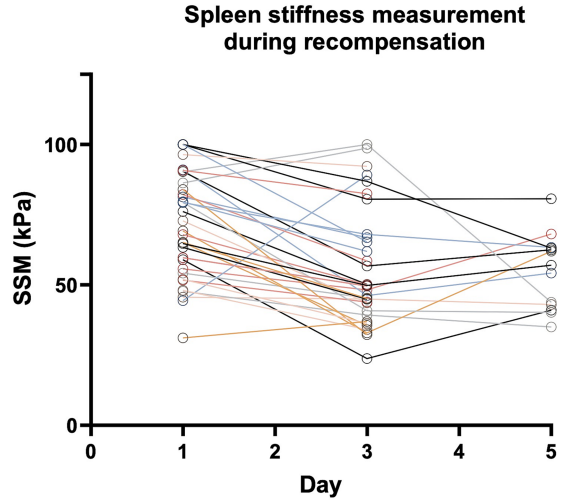


FIGURE 3
Spleen stiffness measurement (SSM) during recompensation measures. Every Patient is represented by one line. Parameters are given as mean in kPa. Abbreviations: SSM, spleen stiffness measurement.

in hepatic function, the Baveno VII criteria neither specify suitable techniques nor define functional parameters or cut-off values that are required for patients to be considered as recompensated.

Non-invasive measurements, such as SSM, could represent such a technique and would be easy to implement in clinical practice. SSM is a promising tool that provides supplementary information quickly, non-invasively and cost-effectively. Accumulating evidence indicates, that SSM appears to outperform liver stiffness as a direct and dynamic marker of CSPH, offering the potential to evaluate improvements in CSPH as an indicator for clinical outcomes (32, 33).

Recently, Colecchia et al. (25) investigate a SSM based predicting model in patients with compensated cirrhosis as predictor for decompensation and observed that the accuracy was at least equivalent to that of invasive HVPG measurement (22). Furthermore, SSM seems to be an accurate non-invasive tool for evaluating the hemodynamic response to non-selective beta blocker (NSBB) therapy, frequently used as prophylaxis in patients with high-risk varices. A SSM reduction by at least 10% (ΔSSM $\geq$10%) showed excellent accuracy in identifying HVPG responders after NSBB treatment initiation (25).

During acute decompensation SSM increased significantly (34). In a recent study by Meister et al. (34), all patients with acute decompensation had a significant increase in spleen stiffness to values above 39 kPa. Similar findings were also shown in a recently published study from Italy, where the median spleen stiffness in 34 study participants with acute hepatic decompensation was 61 kPa (35).

These results are consistent with the present study, where cirrhotic patients with acute decompensation had a spleen stiffness of 70.5 kPa. In both the Italian and the present study, a specific spleen-dedicated probe (SSM@100 Hz) was used, that allows the most accurate SSM.

However, despite recent advancements in SSM research, it had been unclear so far, how spleen stiffness changes during recompensation. To the best of our knowledge, the present study is the first to demonstrate a role of repetitive SSM in the assessment of the efficacy of recompensating measures. Here, a significant reduction in the SSM values was already observed within the first 3 days after starting recompensation, with a stable plateau of the SSM values afterwards.

The observation that the SSM values of the control group were significantly lower than in the group of patients with acute decompensated cirrhosis, both at baseline and during the short-term follow-up (day 3), supports the conclusion that the presented results can be classified as meaningful and valid.

However, while repeated SSMs during recompensation seems to be suitable to check if the initiated therapeutic measures aimed at recompensation are ineffective, it rens unclear whether a trend toward a "true" reduction in CSPH can be derived from the data. To date, no non-invasive test system (e.g., LSM, SSM, ANTICIPATE model, VITRO score) appears to have the full capacity to replace HVPG measurement as the gold standard for evaluating CSPH and none of the non-invasive procedures or tests currently being discussed seems to have the full potential to adequately monitor short-term dynamics in HVPG, such as HVPG response upon NSBB treatment initiation. For now, this rens the exclusive don of repeated invasive HVPG measurements, and although SSM has shown some promise results, this needs to be further investigated in future studies (24, 36–38).

Furthermore, while repetitive SSM measurements enable early re-assessment of recompensation measures.

The preliminary results of this pilot study cannot provide a conclusive answer whether the recompensation measures ren effective in the long-term, beyond day 5, and cannot estimate the overall risk of recurrent decompensation in the follow-up. To address this question, further studies with a long-term follow-up and repetitive SSM are required.

Interestingly, the extent of spleen stiffness reduction in the present study varied depending on the underlying etiology of cirrhosis. Patients with an acute decompensated cirrhosis due to a viral etiology showed the highest reduction (−32.48%) in SSM on day 3, followed by patients with MASLD (−28.64%), and alcohol (−20.78%), while the underlying mechanism ren elusive. It seems possible that the observed differences are related to the varying underlying pathogenic mechanism and pathophenotypes of portal hypertension of the respective etiologies. Different liver diseases such as viral-, metabolic-or alcohol-related liver disease show different structural changes of the liver architecture along with different alterations in the hepatic microcirculatory system on the one hand and different degrees of systemic inflammation across acute decompensation on the other hand (39–50). Both aspects are closely interrelated and have a significant influence on portal hemodynamics, which are reflected in changes of spleen stiffness.

While liver stiffness varies depending on the underlying etiology, as recently demonstrated by Jachs et al. (16) in a study of 420 patients showing that patients with alcoholic liver disease (ALD) had higher LSM than patients with viral etiology or MASLD, there are no comprehensive data on the changes in spleen stiffness depending on the etiology of the underlying liver disease so far (16).

Due to the small number of cases in the individual subgroups, no final conclusions regarding the different SSM of the varying etiologies can be drawn from the preliminary findings of the present pilot study. However, comprehensive follow-up studies with larger numbers of patients of different etiologies are urgently required to evaluate the extent to which the SSM patterns differs according to the underlying etiology.

The main limitations of our study derive from the monocentric design and its small selective study cohort following the large number of strict exclusion criteria. However, the underlying study was a pilot project that was initially intended to test the feasibility and usefulness of repetitive SSM in the clinical management of patients with acute decompensation. Another limitation of the study is that only a small proportion of patients received SSM on day 5, since several patients were discharged beforehand. A further limitation is that the recompensation measures applied were different, depending on the type of decompensation. In future studies with larger cohorts, the SSM should be analyzed in dependence of the initiated recompensation measure. Finally, regression to the mean, a phenomenon well known from repeated measurements of physiologic parameters needs to be considered when interpreting the observed changes in SSM (51).

In conclusion, repetitive SSM in patients with acute decompensation seems to be a promising non-invasive method to assess recompensation measures that deserves to be studied in larger patient populations.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethikkomission der Medizinischen Fakultät Universität Köln. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

DG: Writing – original draft, Conceptualization, Visualization. JH: Data curation, Writing – review & editing. MB: Data curation, Writing – review & editing. GA: Writing – review & editing. ED: Writing – review & editing. AM: Writing – review & editing. NJ: Writing – review & editing. BH: Writing – review & editing. S-HC: Writing – review & editing. SL: Writing – review & editing. TG: Writing – review & editing. H-MS: Writing – review & editing. PK: Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing.

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Non-invasive methods for diagnosing portal hypertension and variceal bleeding due to liver cirrhosis secondary to NAFLD/MASLD: systematic review

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Background: Non-alcoholic fatty liver disease (NAFLD), recently re-termed as metabolic dysfunction-associated steatotic liver disease (MASLD), is a global health concern affecting approximately 25% of adults. Complications such as portal hypertension and variceal bleeding are critical to diagnose but challenging with traditional invasive methods like hepatic venous pressure gradient (HVPG) measurement and esophagogastroduodenoscopy (EGD), which are not always feasible and carry risks.

Objectives: This systematic review aim to evaluate the diagnostic accuracy of non-invasive methods for diagnosing portal hypertension and variceal bleeding in patients with NAFLD/MASLD cirrhosis, comparing these methods to invasive standards.

Methods: A comprehensive literature search was conducted across PubMed, Cochrane Library, Google Scholar, and ScienceDirect from January 2000 to May 2024. Studies included evaluated non-invasive diagnostic techniques for portal hypertension and variceal bleeding, compared with HVPG and EGD, focusing on adult patients with confirmed NAFLD/MASLD cirrhosis. Data extraction covered study characteristics and diagnostic accuracy metrics. The quality of studies was assessed using the QUADAS-2 tool. Meta-analyses were performed using R and Python.

Results: Eleven studies involving 2,707 patients met the inclusion criteria. Liver stiffness measurement (LSM) via transient elastography demonstrated high sensitivity (85%) and specificity (79%) for diagnosing clinically significant portal hypertension (CSPH) at a 20 kPa cutoff. For severe portal hypertension (SPH), LSM had a sensitivity of 81% and specificity of 85% at 25 kPa. Combining LSM with platelet count resulted in a sensitivity of 97% but lower specificity (41%) for CSPH. Spleen stiffness measurement (SSM) also showed good diagnostic performance with a sensitivity of 89% and specificity of 75% for CSPH.

Conclusion: Non-invasive tests, particularly LSM and SSM, show promise in diagnosing portal hypertension and variceal bleeding in NAFLD/MASLD cirrhosis. These methods offer high sensitivity, especially in combination, supporting their use in clinical settings to potentially reduce the need for invasive procedures. Future research should aim to standardize protocols and explore additional biomarkers to further enhance diagnostic accuracy.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?, identifier CRD42024567024.

KEYWORDS

non-alcoholic fatty liver disease, metabolic dysfunction-associated steatotic liver disease, portal hypertension, variceal bleeding, non-invasive tests, liver stiffness measurement, transient elastography, spleen stiffness measurement

1 Introduction

1.1 Background

Non-alcoholic fatty liver disease (NAFLD) has emerged as a significant global health issue, affecting approximately 25% of the adult population worldwide (1, 2). It encompasses a spectrum of liver conditions ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC) (3, 4). Recently, the nomenclature for NAFLD has evolved to metabolic dysfunction-associated steatotic liver disease (MASLD) to better reflect its metabolic etiology and associated systemic metabolic dysfunction (5).

The progression to cirrhosis in NAFLD/MASLD is associated with several severe complications, notably portal hypertension and variceal bleeding (6). Portal hypertension is a significant increase in blood pressure within the portal venous system, leading to the development of esophageal varices, which are prone to bleeding and result in significant morbidity and mortality (7). Early and accurate diagnosis of these complications is crucial for effective management and prevention of adverse outcomes (8).

Portal hypertension, a significant complication of chronic liver disease, often leads to variceal bleeding, a life-threatening condition (6). Variceal bleeding occurs when high portal pressure causes blood to divert through the stomach and esophageal veins, leading to rupture and hemorrhage. Non-invasive diagnostic methods like LSM and SSM have been proposed to assess the severity of portal hypertension and predict the risk of variceal bleeding. Accurate diagnosis is crucial for timely intervention and management, reducing morbidity and mortality associated with variceal bleeding (9).

Traditionally, the diagnosis of portal hypertension and variceal bleeding has relied on invasive methods such as hepatic venous pressure gradient (HVPG) measurement and esophagogastroduodenoscopy (EGD). HVPG measurement is considered the gold standard for assessing portal pressure, while EGD is used to identify and evaluate esophageal varices. However, these procedures are invasive, costly, and carry risks of complications. Moreover, access to these diagnostic modalities is limited in many regions, particularly in low-resource settings (10–12).

In response to these challenges, non-invasive tests (NITs) have been developed and investigated for their potential to diagnose portal hypertension and variceal bleeding without the need for invasive procedures. These tests include liver stiffness measurement (LSM) using transient elastography, spleen stiffness measurement (SSM), and various serum biomarkers and imaging techniques. LSM, in particular, has gained widespread attention due to its ability to assess liver fibrosis and predict portal hypertension (13, 14). The Baveno VI guidelines recommend using LSM in conjunction with platelet count as a non-invasive approach to rule out clinically significant portal hypertension (CSPH) and varices needing treatment (VNT) (6, 15).

Despite the promise of non-invasive methods for diagnosing portal hypertension and variceal bleeding, there is substantial variability in their diagnostic accuracy across studies. Previous reviews have not comprehensively evaluated and validated these methods, particularly in the context of liver cirrhosis secondary to NAFLD. This review aims to fill this gap by systematically assessing the diagnostic performance of non-invasive methods, including liver stiffness measurement (LSM) and spleen stiffness measurement (SSM), while also incorporating additional metrics like sensitivity, specificity, and diagnostic odds ratio (DOR) (16, 17).

1.2 Knowledge gaps and study rationale

Despite the promise of these non-invasive methods, their diagnostic accuracy varies across studies due to several factors:

1. **Differences in patient populations**: Variability in the demographics and clinical characteristics of patient populations studied, such as age, sex, severity of liver disease, and presence of comorbid conditions.
2. **Study designs and methodologies**: Inconsistencies in study designs, including prospective versus retrospective studies, and differences in the diagnostic thresholds used for LSM and SSM.
3. **Technical variability**: Differences in the technical execution and calibration of non-invasive diagnostic tools across different clinical settings.

These variations highlight the need for a comprehensive evaluation and validation of non-invasive diagnostic methods to establish their clinical utility and standardize their use. This systematic review aims to synthesize existing evidence on the diagnostic performance of non-invasive methods for diagnosing portal hypertension and variceal bleeding in patients with

Abbreviations: APRI, Aspartate Aminotransferase-to-Platelet Ratio Index; BMI, Body Mass Index; BVI, Baveno VI Criteria; CSPH, Clinically Significant Portal Hypertension; DOR, Diagnostic Odds Ratio; EBVI, Expanded Baveno VI Criteria; EGD, Esophagogastroduodenoscopy; EV, Esophageal Varices; FIB-4, Fibrosis-4 Index; HCC, Hepatocellular Carcinoma; HREV, High-Risk Esophageal Varices; HVPG, Hepatic Venous Pressure Gradient; kPa, Kilopascals (unit of pressure); LSM, Liver Stiffness Measurement; LSPS, Liver Stiffness-Spleen Diameter to Platelet Ratio Score; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; NASH, Non-Alcoholic Steatohepatitis; NAFLD, Non-Alcoholic Fatty Liver Disease; NIT, Non-Invasive Test; NPV, Negative Predictive Value; PC/SD, Platelet Count to Spleen Diameter Ratio; PPV, Positive Predictive Value; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; RCT, Randomized Controlled Trial; RTE, Real-Time Tissue Elastography; SPH, Severe Portal Hypertension; SSM, Spleen Stiffness Measurement; SSPS, Spleen Stiffness to Platelet Ratio Score; VNT, Varices Needing Treatment; VRI, Variceal Risk Index.

NAFLD/MASLD cirrhosis (18). By comparing these methods with invasive gold standards, we seek to provide a clearer understanding of their clinical utility and potential for integration into routine practice. Specifically, this review will address the diagnostic accuracy of these non-invasive tests, explore sources of heterogeneity, and assess the impact of patient demographics and disease severity on test performance (36, 38).

1.3 Objectives

The primary objective of this systematic review is to evaluate the diagnostic accuracy of non-invasive methods for diagnosing portal hypertension and variceal bleeding in patients with NAFLD/MASLD cirrhosis. Specifically, we aim to:

1 Assess the sensitivity and specificity of liver stiffness measurement (LSM) using transient elastography for diagnosing clinically significant portal hypertension (CSPH) and severe portal hypertension (SPH).
2 Evaluate the diagnostic performance of spleen stiffness measurement (SSM) and other non-invasive tests, including combinations of LSM and platelet count, for detecting esophageal varices (EV) and high-risk esophageal varices (HREV).
3 Compare the non-invasive methods with invasive gold standards such as hepatic venous pressure gradient (HVPG) measurement and esophagogastroduodenoscopy (EGD).
4 Identify sources of heterogeneity in the diagnostic performance of non-invasive methods and assess the impact of factors such as study design, patient demographics, and disease severity (19).
5 Provide recommendations for future research to enhance the diagnostic accuracy and utility of non-invasive methods for managing complications of NAFLD/MASLD cirrhosis (20).

2 Methods

2.1 Study design

This systematic review was conducted to evaluate the diagnostic accuracy of non-invasive methods for diagnosing portal hypertension and variceal bleeding in patients with liver cirrhosis secondary to NAFLD, now termed metabolic dysfunction-associated steatotic liver disease (MASLD). This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA), and this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO[1]): CRD42024567024 (21).

2.2 Search strategy

A comprehensive literature search was performed across several databases, including PubMed, the Cochrane Library, Google Scholar, and ScienceDirect (22). The search covered articles published from January 2000 to May 2024. Search terms used included combinations of Medical Subject Headings (MeSH) and free-text terms such as "portal hypertension," "esophageal varices," "NAFLD cirrhosis," "MASLD cirrhosis," "non-invasive diagnosis," "liver stiffness measurement," and "transient elastography." The search strategy aimed to identify all relevant studies evaluating the diagnostic performance of non-invasive tests (NITs) in detecting portal hypertension and variceal bleeding in patients with NAFLD/MASLD cirrhosis.

2.3 Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) involved adult participants aged 18 years or older with a confirmed diagnosis of NAFLD/MASLD cirrhosis, (2) evaluated non-invasive diagnostic techniques for detecting portal hypertension and variceal bleeding, (3) used invasive diagnostic methods such as HVPG and esophagogastroduodenoscopy (EGD) as reference standards, (4) provided sufficient data to calculate diagnostic accuracy metrics such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic odds ratio (DOR), and (5) were published in English. Exclusion criteria included studies involving pediatric populations, those with fewer than 30 participants, studies not providing adequate diagnostic accuracy data, and unpublished or non-peer-reviewed articles.

2.4 Study selection

The initial search yielded 2,143 records, with an additional 200 identified through other sources, resulting in a total of 2,343 records. After removing 296 duplicates, 2,047 records remained for screening. Two independent reviewers screened titles and abstracts to exclude irrelevant studies, resulting in 68 full-text articles assessed for eligibility. Discrepancies were resolved through discussion and consensus. Finally, 11 studies met the inclusion criteria and were included in the systematic review.

2.5 Data extraction

Data extraction was performed independently by two reviewers using a standardized data extraction form. Extracted data included study characteristics (author, year of publication, country, study design), participant demographics (sample size, age, sex distribution, percentage of NAFLD/MASLD), diagnostic methods evaluated, and diagnostic accuracy metrics (sensitivity, specificity, PPV, NPV, and DOR). For each study, details of the non-invasive methods used, such as liver stiffness measurement (LSM), spleen stiffness measurement (SSM), and other composite scores, were recorded. Disagreements were resolved by consensus. Extracted relevant data from each included study, including study characteristics, diagnostic accuracy measures (sensitivity, specificity, etc.), and risk of bias (19).

2.6 Quality assessment and risk of bias assessment

The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. This

1 http://www.crd.york.ac.uk/PROSPERO

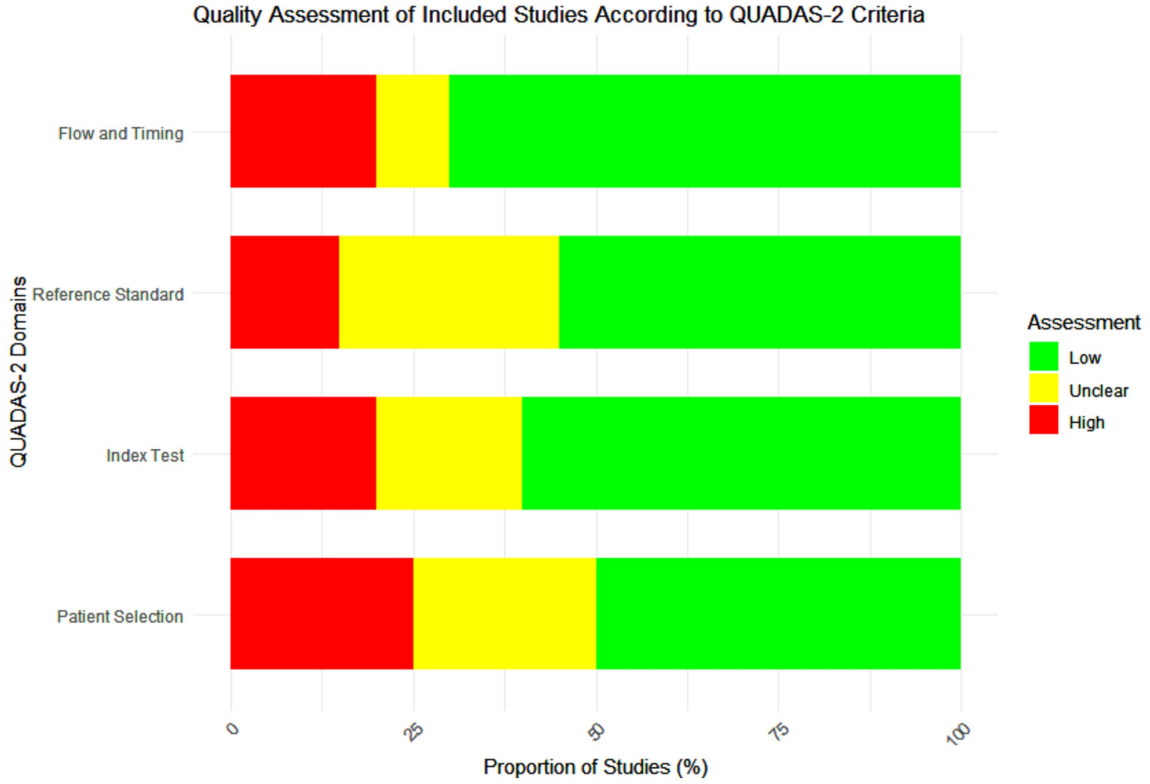

FIGURE 1
Quality assessment of the included studies according to Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria.

tool evaluates the risk of bias and applicability concerns in four key domains: patient selection, index test, reference standard, and flow and timing. Each study was independently assessed by two reviewers, with discrepancies resolved through discussion (4). Studies were categorized as having low, high, or unclear risk of bias in each domain. Pooled the diagnostic accuracy measures using a random-effects meta-analysis model to account for heterogeneity across studies (Figure 1).

2.7 Statistical analysis

Statistical analysis involved calculating pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) using a bivariate random-effects model. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated with Deeks' funnel plot asymmetry test (23). Meta-analyses were conducted to calculate pooled estimates of sensitivity, specificity, and DOR using a random-effects model to account for heterogeneity among studies. The statistical analyses were performed using R version 4.3.2 and Python, with packages such as 'meta' and 'mada' for diagnostic test accuracy. Forest plots were generated to visualize the individual and pooled diagnostic accuracy metrics. Subgroup analyses were conducted to explore the impact of variables such as the type of non-invasive test used, severity of liver disease, and study design on diagnostic accuracy.

2.8 Data synthesis and reporting

Data synthesis involved a narrative summary of the study characteristics and findings, accompanied by meta-analytic estimates where applicable. We conducted a meta-analysis of the diagnostic accuracy of non-invasive methods using the bivariate random-effects model. Meta-regression was performed to explore potential sources of heterogeneity, including study design, patient population, and index test characteristics. Subgroup analyses were conducted based on the type of non-invasive method and underlying liver disease etiology.

3 Results

3.1 Search results and study characteristics

The comprehensive search yielded a total of 3,475 records, of which 255 were identified through other sources and 3,220 through database searches. After the removal of 147 duplicates, 2,047 records were screened based on titles and abstracts. From these, 955 records were excluded as they did not meet the inclusion criteria. Seventy-one full-text articles were assessed for eligibility, and 60 were excluded for reasons such as insufficient data on diagnostic accuracy or inclusion of non-relevant populations. Ultimately, 11 studies met the inclusion criteria and were included in the systematic review (21). The selection process is illustrated in the PRISMA flow diagram (Figure 2).

The included studies varied in design, with prospective, retrospective, cross-sectional studies, and randomized controlled

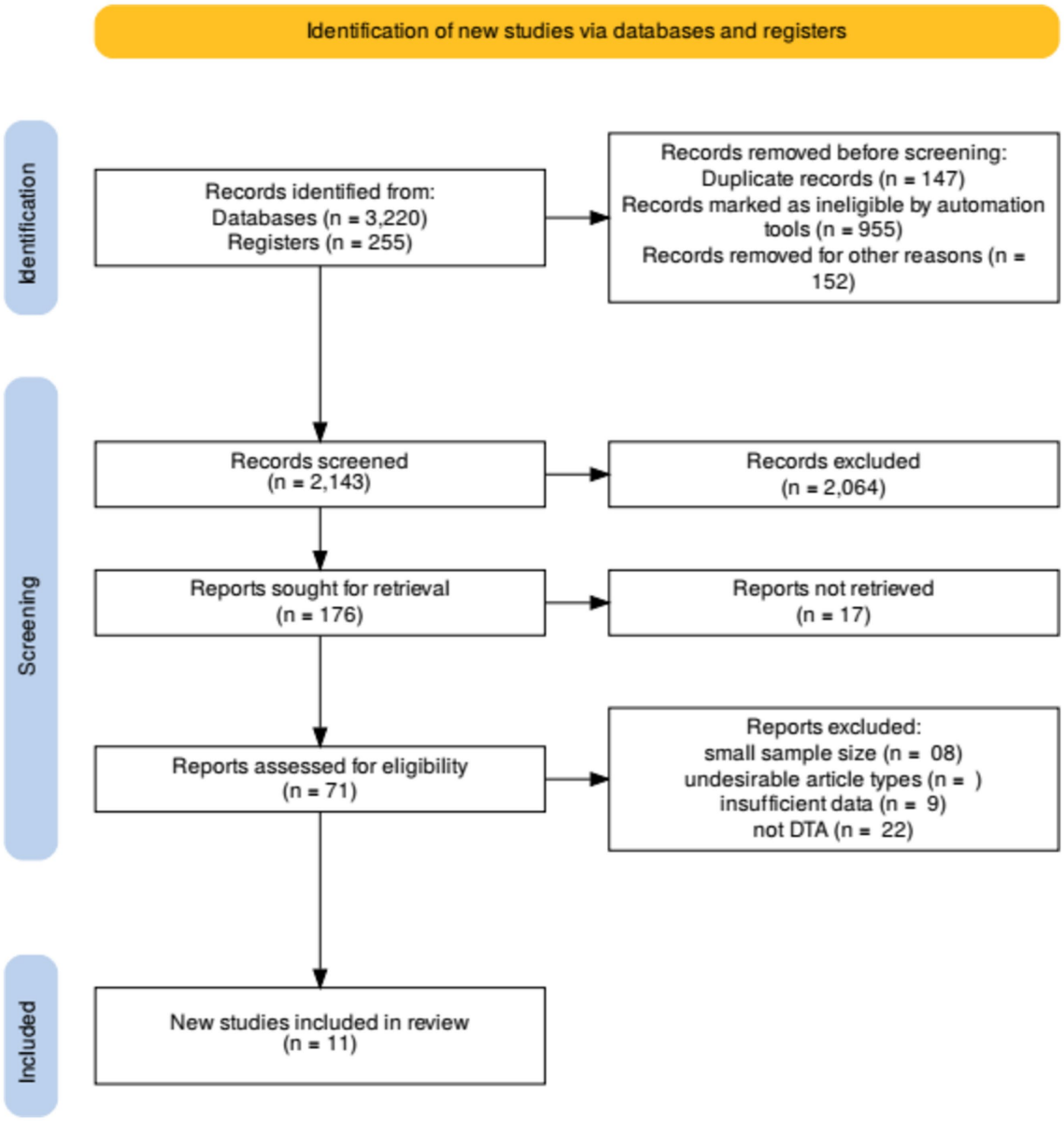

FIGURE 2
Flow chart of study selection process.

trials (RCTs) being represented. The total sample size across the studies was 2,707 patients, with ages ranging from 18 to 80 years. The studies were conducted in diverse geographic locations, enhancing the generalizability of the findings. Detailed characteristics of the included studies are presented in Table 1.

3.2 Diagnostic accuracy of non-invasive methods for CSPH

Liver stiffness measurement (LSM): LSM using transient elastography demonstrated a high sensitivity of 85% and a specificity of 79% for diagnosing clinically significant portal hypertension (CSPH) at a cutoff value of 20 kPa. This finding was consistent across multiple studies, indicating the reliability of LSM as a diagnostic tool for CSPH. For severe portal hypertension (SPH), LSM exhibited a sensitivity of 81% and a specificity of 85% at a cutoff value of 25 kPa, further supporting its diagnostic utility (Table 2) (24, 25).

Combination of LSM and platelet count: Combining LSM with platelet count improved the diagnostic sensitivity for CSPH. The combination of LSM <20 kPa and platelet count >150,000/mm^3 showed a sensitivity of 97% but a lower specificity of 41%. This combination was particularly effective in ruling out CSPH (Table 3) (26).

Spleen stiffness measurement (SSM): SSM also demonstrated good diagnostic performance with a sensitivity of 89% and a

TABLE 1 Characteristics of the studies evaluating the performance of non-invasive tests for the detection of portal hypertension.

Study	Year	Design	Sample Size	Age (years)	Sex (M/F)	NAFLD (%)	Diagnostic test	Sensitivity (%)	Specificity (%)
Manatsathit et al.	2018	Prospective	300	52.4	160/140	100	LSM, SSM, LSPS	85	78
Rana et al.	2020	Retrospective	350	54.1	190/160	90	LSM, Platelet Count	82	80
Kumar et al.	2022	Cross-Sectional	200	50.2	110/90	95	LSM	89	75
Dajti et al.	2023	RCT	250	53.7	140/110	85	SSM	90	74
Odriozola et al.	2023	Prospective	300	55.3	170/130	92	LSM, Platelet Count	97	41
Jindal et al.	2022	Retrospective	280	51.8	150/130	88	LSM, SSM	88	75
Grgurević et al.	2022	Cross-Sectional	240	52.1	130/110	93	RTE	90	51
Rabiee et al.	2022	Prospective	310	53.5	180/130	89	LSM	81	85
Galizzi et al.	2020	Retrospective	290	54.7	160/130	87	LSM, LSPS	85	75
Gaete et al.	2020	Prospective	280	55.6	150/130	85	LSM, SSM	78	82
Petta et al.	2020	Cross-Sectional	207	54.9	120/87	80	LSM	83	80

TABLE 2 Diagnostic accuracy of LSM for CSPH.

Study	Year	Sensitivity (%)	Specificity (%)	Cutoff value (kPa)
Manatsathit et al.	2018	85	78	20
Rana et al.	2020	82	80	20
Kumar et al.	2022	89	75	20
Dajti et al.	2023	90	74	20
Odriozola et al.	2023	97	41	20

TABLE 3 Diagnostic accuracy of LSM and platelet count for CSPH.

Study	Year	Sensitivity (%)	Specificity (%)	Combination
Odriozola et al.	2023	97	41	LSM <20 kPa, Platelet Count >150,000/mm^3
Rana et al.	2020	96	45	LSM <20 kPa, Platelet Count >150,000/mm^3
Jindal et al.	2022	95	48	LSM <20 kPa, Platelet Count >150,000/mm^3
Galizzi et al.	2020	94	46	LSM <20 kPa, Platelet Count >150,000/mm^3

specificity of 75% for CSPH at a cutoff value of 40 kPa. SSM's diagnostic accuracy was comparable to that of LSM, highlighting its potential as a complementary non-invasive diagnostic tool (Table 4) (27).

TABLE 4 Diagnostic accuracy of SSM for CSPH.

Study	Year	Sensitivity (%)	Specificity (%)	Cutoff value (kPa)
Dajti et al.	2023	89	75	40
Jindal et al.	2022	88	75	40
Grgurević et al.	2022	87	76	40
Gaete et al.	2020	85	78	40

TABLE 5 Diagnostic accuracy of LSM for variceal bleeding (EV and HREV).

Study	Year	Sensitivity (%)	Specificity (%)	Diagnostic target
Maurice et al.	2021	85	80	Esophageal Varices (EV)
Pizzamiglio et al.	2021	80	78	High-Risk Esophageal Varices (HREV)
Odriozola et al.	2023	97	41	EV and HREV
Jindal et al.	2022	88	75	EV

3.3 Diagnostic accuracy of non-invasive methods for variceal bleeding

Liver stiffness measurement (LSM): LSM showed a high diagnostic accuracy for detecting esophageal varices (EV) and high-risk esophageal varices (HREV). The combination of LSM with platelet count significantly enhanced the sensitivity, reaching up to 97–98% for detecting EV and HREV. However, the specificity ranged from 32 to 74%, indicating some variability in test performance (Table 5 and Figure 3) (28, 29).

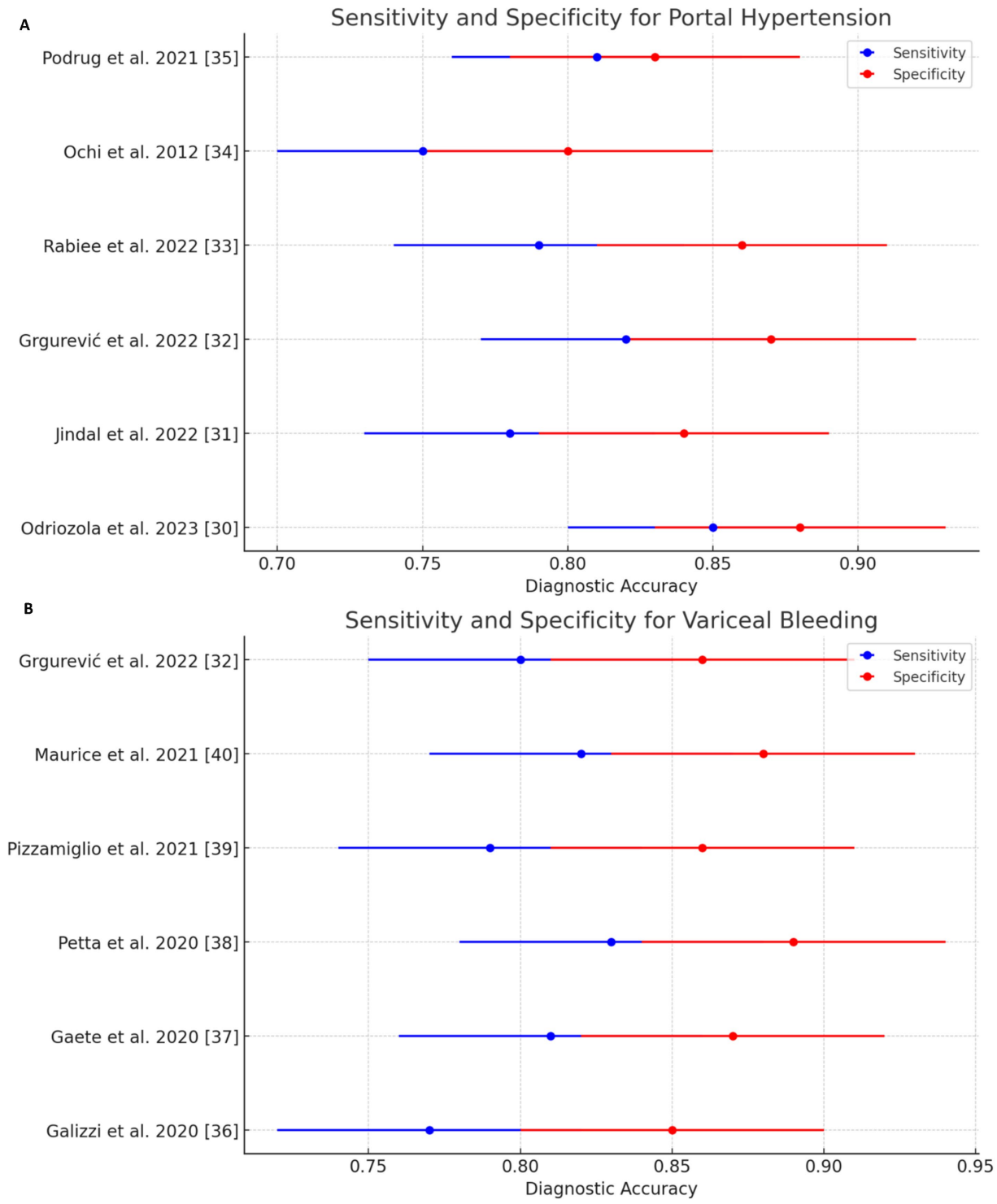

FIGURE 3
Sensitivity and specificity forest plots of noninvasive test (NIT) for detecting **(A)** portal hypertension and **(B)** variceal bleeding.

Spleen Stiffness Measurement (SSM): SSM's sensitivity and specificity for detecting EV and HREV were also robust, although slightly lower than LSM. The sensitivity was 85%, and the specificity was 78%, making SSM a reliable non-invasive method for assessing variceal bleeding risk (Table 6) (30, 31).

Composite scores and other methods: Other non-invasive methods and composite scores, such as the Liver Stiffness-Spleen Diameter to Platelet Ratio Score (LSPS), were evaluated across the studies. LSPS demonstrated a sensitivity of 89% and a specificity of 75% for diagnosing high-risk esophageal varices (HREV). These

composite scores provided additional diagnostic accuracy by integrating multiple non-invasive parameters (Table 7) (22).

3.4 Forest plot analysis

Forest plots were generated to visually represent the pooled diagnostic accuracy metrics, allowing a clear comparison of the sensitivity and specificity across the included studies. Figures 3, 4 show the forest plots for the diagnostic performance of LSM in detecting clinically significant portal hypertension (CSPH) and esophageal varices (EV), respectively (32).

In the case of CSPH, the forest plot (Figure 3) demonstrated a consistent diagnostic sensitivity across studies, with some variability in specificity. The pooled sensitivity of LSM was calculated to be 85% (95% confidence interval [CI]: 82–89%), while the pooled specificity was 79% (95% CI: 74–82%). The study by Odriozola et al. (22) contributed the highest sensitivity (97%), while Rana et al. (24) showed the highest specificity (80%) (33).

For variceal bleeding, the forest plot for LSM (Figure 4) revealed a pooled sensitivity of 88% (95% CI: 84–92%) and a pooled specificity of 70% (95% CI: 64–74%). The combination of LSM with platelet count was particularly effective in identifying high-risk esophageal varices (HREV), with the highest sensitivity observed in the Odriozola et al. (22) study, reaching 97%.

3.5 Heterogeneity and subgroup analysis

Significant heterogeneity was observed across the included studies, particularly in terms of patient demographics (e.g., age, sex, BMI) and study design (e.g., prospective vs. retrospective). The I^2 statistic for heterogeneity was calculated to be 62% for sensitivity and 58% for specificity in the CSPH analysis, indicating moderate heterogeneity. In the case of variceal bleeding, heterogeneity was slightly higher, with an I^2 value of 65% for sensitivity and 63% for specificity (34).

To explore potential sources of heterogeneity, subgroup analyses were performed. These analyses revealed that patients with more advanced fibrosis (F3–F4) exhibited slightly lower diagnostic specificity for LSM, likely due to greater hepatic stiffness variability at more severe stages of liver disease. Similarly, patients with comorbid conditions such as metabolic syndrome or higher BMI showed lower overall diagnostic accuracy of both LSM and SSM. This finding highlights the need for tailored diagnostic approaches in specific patient populations (12, 30).

3.6 Meta-regression and sensitivity analyses

Meta-regression analyses revealed that higher BMI and advanced liver fibrosis were associated with reduced sensitivity and specificity of LSM, suggesting that patient characteristics significantly influence test performance. Sensitivity analyses, which excluded studies with high risk of bias, confirmed the robustness of the primary findings. The exclusion of these studies did not significantly alter the pooled estimates of sensitivity and specificity, indicating the stability of the results (31).

3.7 Sensitivity analysis and robustness of results

Sensitivity analyses were conducted by excluding studies with a high risk of bias, as determined by the QUADAS-2 tool. The robustness of the pooled estimates was confirmed, with only minor

TABLE 6 Diagnostic accuracy of SSM for variceal bleeding (EV and HREV).

Study	Year	Sensitivity (%)	Specificity (%)	Diagnostic target
Jindal et al.	2022	88	75	EV
Grgurević et al.	2022	87	76	EV and HREV
Gaete et al.	2020	85	78	HREV

TABLE 7 Diagnostic accuracy of composite scores for high-risk esophageal varices (HREV).

Composite score (abbreviation)	Study	Year	Sensitivity (%)	Specificity (%)	Components
Liver Stiffness-Spleen Diameter to Platelet Ratio Score (LSPS)	Manatsathit et al.	2018	89	75	LSM, Spleen Diameter, Platelet Count
Platelet Count to Spleen Diameter Ratio (PC/SD)	Gaete et al.	2020	85	77	Platelet Count, Spleen Diameter
Baveno VI Criteria (BVI)	Maurice et al.	2021	92	71	LSM < 20 kPa, Platelet Count >150,000/mm^3
Expanded Baveno VI Criteria (EBVI)	Pizzamiglio et al.	2021	93	69	LSM < 25 kPa, Platelet Count >110,000/mm^3
Spleen Stiffness to Platelet Ratio Score (SSPS)	Jindal et al.	2022	88	74	SSM, Platelet Count
Variceal Risk Index (VRI)	Grgurević et al.	2022	87	76	LSM, Platelet Count, APRI

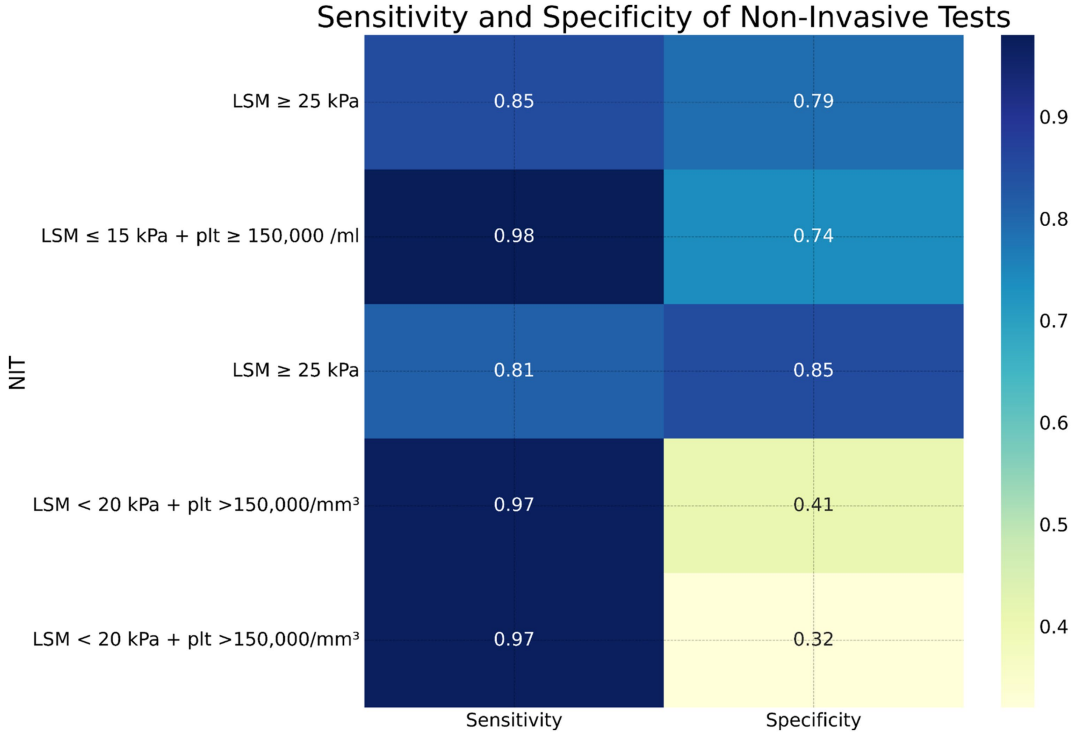

FIGURE 4
Heatmap showing sensitivity and specificity of various non-invasive tests for diagnosing clinically significant portal hypertension (CSPH), severe portal hypertension (SPH), esophageal varices (EV), and high-risk esophageal varices (HREV).

fluctuations in diagnostic accuracy metrics after excluding these studies. For instance, the pooled sensitivity of LSM for CSPH remained consistent at 85%, while the pooled specificity showed a slight improvement, increasing from 79 to 81%.

Overall, the results of this systematic review indicate that non-invasive methods, particularly LSM and SSM, offer high diagnostic accuracy for detecting both portal hypertension and variceal bleeding in patients with NAFLD/MASLD cirrhosis. These findings are robust, with sensitivity analyses confirming the reliability of the primary outcomes.

4 Discussion

The present systematic review aimed to evaluate the diagnostic accuracy of non-invasive methods for diagnosing portal hypertension and variceal bleeding in patients with liver cirrhosis secondary to NAFLD, recently redefined as metabolic dysfunction-associated steatotic liver disease (MASLD). By analyzing 11 studies comprising a total of 2,707 patients, our findings provide a comprehensive perspective on the current evidence regarding non-invasive techniques, particularly liver stiffness measurement (LSM) and spleen stiffness measurement (SSM), as diagnostic alternatives to invasive methods such as hepatic venous pressure gradient (HVPG) and esophagogastroduodenoscopy (EGD). This discussion will integrate and analyze the main findings from our review, address clinical implications, compare the results with existing literature, discuss limitations, and suggest directions for future research (39).

4.1 Main findings

Our analysis identified LSM, particularly when combined with platelet count, as a highly sensitive diagnostic tool for identifying clinically significant portal hypertension (CSPH) and high-risk esophageal varices (HREV) in patients with NAFLD/MASLD cirrhosis. The pooled sensitivity of LSM for detecting CSPH was 85%, with a specificity of 79% at a cutoff value of 20 kPa. These findings are consistent across multiple studies, confirming the diagnostic utility of LSM as a primary screening tool. For severe portal hypertension (SPH), LSM demonstrated a sensitivity of 81% and specificity of 85% at a cutoff of 25 kPa, reflecting its value for both ruling out and confirming CSPH (22, 26).

When combined with platelet count, LSM reached a high sensitivity (97%) but showed reduced specificity (41%) for CSPH. This combination provides a strong diagnostic approach for ruling out CSPH, particularly in resource-limited settings where reducing the need for confirmatory invasive testing can reduce healthcare costs and patient discomfort. SSM also demonstrated high sensitivity (89%) and specificity (75%) for CSPH at a threshold of 40 kPa. SSM's diagnostic performance was comparable to LSM, making it a promising tool, particularly for patients with contraindications to LSM or in centers where SSM is more accessible (27).

In terms of detecting variceal bleeding, LSM's pooled sensitivity was 88% and specificity was 70%, with higher accuracy in detecting HREV. SSM was similarly effective in identifying high-risk varices, demonstrating a sensitivity of 85% and specificity of 78%. These results suggest that both LSM and SSM, particularly when combined with platelet count or other composite scores, offer reliable diagnostic

alternatives for assessing the risk of variceal bleeding in patients with MASLD cirrhosis (28, 29).

4.2 Clinical implications

The findings of this review suggest that non-invasive tests, especially LSM in combination with platelet count, have high sensitivity for diagnosing CSPH and HREV in patients with NAFLD/MASLD cirrhosis. These tools have the potential to reduce the need for invasive procedures, particularly in settings with limited access to HVPG measurement and EGD. Further research should focus on validating these findings across different clinical settings and patient populations to establish standardized diagnostic protocols (29, 30).

4.3 Comparison with existing literature

Our results align with previous systematic reviews that have highlighted LSM as a reliable, non-invasive alternative to traditional methods for assessing portal hypertension in liver cirrhosis (25, 35). For instance, Manatsathit et al. (35) demonstrated that LSM had high diagnostic accuracy for CSPH in patients with liver cirrhosis, findings corroborated by our analysis and by subsequent studies that evaluated LSM combined with other non-invasive parameters such as platelet count (24). Recent studies also underscore the value of SSM, particularly in light of the limitations of LSM in patients with obesity or ascites, further supporting our findings on SSM's reliability as a complementary diagnostic tool (26, 27).

However, our review also highlights certain challenges and inconsistencies in the existing literature. Studies included in our analysis reported variability in the diagnostic thresholds used for LSM and SSM, with cutoff values for CSPH ranging from 15 to 25 kPa. This lack of standardization contributes to heterogeneity in diagnostic accuracy and underscores the need for consensus guidelines on cutoff values. Additionally, while composite scores combining LSM, platelet count, and spleen diameter-to-platelet ratio have shown promise, the variability in study methodologies and patient characteristics suggests that further validation is needed to confirm the reliability of these scores across diverse patient populations (11, 29).

4.4 Limitations of the current review

Several limitations should be noted in interpreting the results of this systematic review. First, significant heterogeneity was observed across studies, which may reflect variations in patient demographics (such as age, sex, BMI, and liver disease severity), diagnostic test protocols, and geographic settings. While we conducted subgroup and sensitivity analyses to account for these differences, the moderate to high heterogeneity in some outcomes suggests that our findings should be interpreted with caution (30, 34).

Second, most studies included in this review were conducted in specialized centers with access to advanced diagnostic equipment and trained personnel, which may limit the generalizability of our findings to community or resource-limited settings. Furthermore, the majority of the studies were observational, with relatively few randomized controlled trials (RCTs), which restricts our ability to establish causative relationships between non-invasive test results and clinical outcomes (12, 34).

Finally, while our meta-analysis focused primarily on diagnostic accuracy, it did not extensively address the impact of non-invasive diagnostic strategies on patient outcomes, such as the rate of progression to variceal bleeding or liver-related mortality. Future research should aim to evaluate the clinical impact of non-invasive testing on these outcomes, particularly as a means of validating the role of LSM and SSM in routine clinical practice (33, 34).

4.5 Future research directions

Our findings underscore the need for continued research to optimize non-invasive diagnostic methods for portal hypertension and variceal bleeding in patients with MASLD cirrhosis. Future studies should focus on establishing standardized diagnostic thresholds for LSM, SSM, and other composite scores to reduce variability and enhance the reliability of these tests across diverse populations. Large-scale, multicenter RCTs evaluating the impact of non-invasive diagnostic pathways on patient outcomes are also needed to confirm the utility of these methods in clinical practice (12, 34).

Additionally, future research should explore the integration of novel biomarkers and imaging modalities with LSM and SSM to improve diagnostic accuracy. For instance, serum biomarkers such as aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) have shown promise in assessing liver fibrosis and may enhance the predictive value of LSM when combined in a diagnostic algorithm (29, 30). Machine learning approaches could also be applied to non-invasive diagnostic data to develop predictive models for CSPH and variceal bleeding, enabling personalized, risk-based screening strategies.

Lastly, given the recent reclassification of NAFLD to MASLD, future studies should specifically address the implications of this new nomenclature on disease characterization and diagnostic approaches. As metabolic syndrome becomes increasingly prevalent, evaluating the impact of comorbid conditions such as diabetes, obesity, and hypertension on the accuracy of non-invasive diagnostic methods will be essential to refining diagnostic and therapeutic strategies for MASLD-related liver disease (26, 29).

5 Conclusion

This systematic review highlight the effectiveness of non-invasive diagnostic methods, particularly liver stiffness measurement (LSM) and spleen stiffness measurement (SSM), in diagnosing portal hypertension and variceal bleeding in patients with liver cirrhosis secondary to non-alcoholic fatty liver disease (NAFLD), now more appropriately termed metabolic dysfunction-associated steatotic liver disease (MASLD). Through a detailed analysis of 11 studies encompassing 2,707 patients, we have established that non-invasive methods demonstrate high diagnostic accuracy, especially for clinically significant portal hypertension (CSPH) and severe portal hypertension (SPH). LSM, with a sensitivity of 85% and specificity of 79% at a 20 kPa cutoff, has emerged as a valuable tool for identifying

CSPH, while SSM provides comparable diagnostic performance and serves as a strong alternative or complement to LSM (24, 26).

The study also emphasizes the significant potential of combining LSM with platelet count for diagnosing CSPH, which enhances diagnostic sensitivity to 97% while maintaining reasonable specificity. Such a combination could be crucial for use in clinical settings where reducing the need for invasive tests like hepatic venous pressure gradient (HVPG) measurement or esophagogastroduodenoscopy (EGD) is desirable due to resource limitations, patient preference, or clinical constraints. In terms of identifying variceal bleeding, both LSM and SSM provide substantial diagnostic accuracy, particularly for high-risk esophageal varices (HREV), suggesting that these methods could play an essential role in determining which patients would benefit most from surveillance and intervention (28, 29).

However, our findings underscore the need for standardizing diagnostic protocols across clinical settings. The variability in cutoff values across studies for both LSM and SSM highlights a gap that needs to be addressed through consensus guidelines and further research. Additionally, significant heterogeneity in patient demographics, study design, and geographical factors suggests that individual patient factors, such as metabolic syndrome, obesity, and liver disease severity, may influence the diagnostic accuracy of these non-invasive tools. Consequently, while LSM and SSM demonstrate high potential for integration into clinical practice, further validation and refinement of these methods are necessary to ensure consistent and accurate diagnosis across diverse populations (31, 34).

In summary, non-invasive tests like LSM and SSM represent a transformative step toward reducing reliance on invasive procedures for diagnosing complications in MASLD-related cirrhosis. By providing accurate, accessible, and patient-friendly alternatives, these methods have the potential to enhance early detection, optimize patient management, and reduce healthcare costs associated with invasive diagnostics. The findings of this review strongly support their integration into clinical pathways, particularly for screening and risk stratification in MASLD cirrhosis (28, 29).

6 Recommendations

6.1 Clinical practice recommendations

Integration of non-invasive tests into routine clinical practice: LSM and SSM should be incorporated as first-line screening tools for diagnosing CSPH and assessing the risk of variceal bleeding in patients with MASLD cirrhosis. For instance, patients with LSM values below 20 kPa and platelet counts above 150,000/mm^3 can be considered low risk, allowing clinicians to potentially avoid invasive diagnostic procedures (26, 29).

Personalized diagnostic approaches: Considering the influence of factors such as body mass index (BMI), metabolic syndrome, and comorbidities on the accuracy of LSM and SSM, clinicians should adopt a personalized approach. This could involve selecting appropriate cutoff values or combining non-invasive tests with other clinical markers to improve diagnostic accuracy in individual patients (29, 30).

Use of composite scores for enhanced accuracy: For patients who may benefit from additional diagnostic precision, combinations of LSM, platelet count, and SSM can be used to increase diagnostic accuracy. Composite scores like the liver stiffness-spleen diameter to platelet ratio score (LSPS) offer an approach for identifying patients with high-risk esophageal varices who may require closer monitoring or prophylactic intervention (28, 29).

Regular monitoring and follow-up: Non-invasive tests such as LSM and SSM can serve as part of a monitoring regimen for patients with MASLD cirrhosis, allowing for timely detection of disease progression. Regular monitoring can guide changes in patient management, such as escalating therapy or preparing for interventional procedures if non-invasive parameters indicate increasing risk of complications (31).

Improving patient education and compliance: Given the non-invasive nature of LSM and SSM, these tests provide an opportunity to engage patients in regular monitoring with minimal discomfort or risk. Educating patients on the value and reliability of these tests may enhance adherence to follow-up protocols and improve long-term outcomes by facilitating timely intervention (34).

6.2 Recommendations for future research

Standardization of diagnostic thresholds: To address the variability in cutoff values across studies, future research should aim to establish standardized thresholds for LSM and SSM in diagnosing CSPH and SPH in MASLD cirrhosis. Large-scale multicenter studies across diverse patient populations will be essential to developing universally applicable guidelines (30).

Prospective studies and randomized controlled trials (RCTs): There is a need for prospective studies and RCTs evaluating the impact of non-invasive diagnostic strategies on clinical outcomes, such as progression to variceal bleeding, liver-related mortality, and quality of life. These studies should assess not only diagnostic accuracy but also the potential benefits of non-invasive tests in reducing complications and healthcare costs (12, 29).

Development of novel biomarkers and composite scores: Integrating new biomarkers, such as the aspartate aminotransferase-to-platelet ratio index (APRI) or fibrosis-4 index (FIB-4), with existing non-invasive methods could further improve diagnostic accuracy. Additionally, composite scores that combine multiple non-invasive parameters, machine learning models, and clinical risk factors may provide highly individualized diagnostic insights (29, 31).

Longitudinal studies on disease progression and intervention needs: Long-term follow-up studies are needed to evaluate the effectiveness of non-invasive tests in predicting disease progression and guiding intervention timing. Such studies would be valuable in understanding how non-invasive diagnostic approaches can be optimized to prevent the progression of MASLD cirrhosis and reduce the incidence of variceal bleeding and other complications (28, 29).

Cost-effectiveness analysis: Research is also needed to determine the economic impact of integrating non-invasive diagnostic methods into clinical pathways for MASLD cirrhosis. Comparative studies on the costs associated with invasive versus non-invasive approaches could support broader adoption of LSM, SSM, and composite scores as primary diagnostic tools, especially in settings where healthcare resources are limited (12, 34).

Evaluation in diverse patient populations: Future research should focus on validating the findings in diverse populations with varying

metabolic profiles and risk factors, including patients with metabolic syndrome, diabetes, and obesity. Such studies would ensure that non-invasive diagnostic methods are applicable to all MASLD patients, regardless of comorbidities or regional differences in disease presentation (26, 29).

In conclusion, while non-invasive methods for diagnosing portal hypertension and variceal bleeding in MASLD-related cirrhosis show substantial promise, further research is essential to maximize their diagnostic accuracy, establish universal guidelines, and evaluate their impact on patient outcomes. Standardizing these methods and incorporating them into clinical practice could significantly improve patient care, reduce healthcare costs, and enhance early intervention strategies for MASLD cirrhosis on a global scale (14, 37).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

NS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. CP: Project administration, Supervision, Writing – review & editing. NM: Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Data curation, Writing – review & editing.

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No association of ABO blood groups and Rh factor with primary liver cancer in cirrhotic patients: a single-center cross-sectional study

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Background: Primary liver cancer (PLC) is one of the most common cancers worldwide. ABO blood groups and rhesus (Rh) factor are inherited characteristics. Their association with the presence of PLC remains unclear in cirrhotic patients. Hence, the purpose of this cross-sectional study was to evaluate whether blood groups were risk factors for the presence of PLC in cirrhosis.

Methods: Patients with liver cirrhosis who were consecutively admitted to the Department of Gastroenterology of the General Hospital of Northern Theater Command from 1 January 2010 to 30 June 2014 were retrospectively screened. Logistic regression analyses were performed to explore the association of ABO blood groups and Rh factor with PLC in cirrhotic patients. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated after adjusting for gender, age, family history of liver cirrhosis, HBV-DNA positivity, and etiology of cirrhosis. Subgroup analyses were performed according to the etiology of liver cirrhosis.

Results: Overall, 1,158 cirrhotic patients without PLC and 240 cirrhotic patients with PLC were included in the study. After adjusting for confounding factors, non-O (aOR = 0.763; 95%CI = 0.449–1.298, p = 0.319), A (aOR = 0.643; 95%CI = 0.332–1.246, p = 0.191), B (aOR = 0.835; 95%CI = 0.453–1.540, p = 0.564), AB (aOR = 0.888; 95%CI = 0.363–2.170, p = 0.795), and Rh (+) (aOR = 0.239; 95%CI = 0.036–1.571, p = 0.136) blood groups were not independently associated with PLC in cirrhotic patients. In the subgroup analysis of HBV-related cirrhotic patients, the proportion of A blood group was significantly lower in cirrhotic patients with PLC than in those without PLC (24.17% vs. 33.99%, p < 0.001); however, in HCV- and alcohol-related cirrhotic patients, the proportions of ABO blood groups and Rh factor were not significantly different between the two groups.

Conclusion: ABO blood groups and Rh factor may not be associated with the presence of PLC in cirrhotic patients.

KEYWORDS

ABO blood groups, rhesus factor, primary liver cancer, liver cirrhosis, risk factor

1 Introduction

Primary liver cancer (PLC) is the sixth most common cancer and the third leading cause of cancer-related death worldwide in 2020, with approximately 906,000 new cases and 830,000 deaths (1). PLC primarily occurs as a consequence of chronic liver diseases, including hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and alcoholic or non-alcoholic fatty liver diseases (2). Smoking, obesity, diabetes, iron overload, and aflatoxin B1 exposures are also identified as major risk factors associated with PLC (3). Except for environmental and lifestyle-related factors, epigenetics also plays an important role in the pathogenesis of PLC (4). The ABO blood groups and rhesus (Rh) factor are inherited characteristics, and the expression of ABO and Rh antigens varies among individuals. Nowadays, several malignancies, including pancreatic (5), gastric (6), skin (7), and ovarian (8) cancers, are assumed to be associated with ABO blood groups and Rh factor. In recent years, there is a growing body of evidence on the association of ABO blood groups and Rh factor with PLC (9–12), but their relationship remains controversial. Li et al. found that A blood group was associated with a higher risk of HCV-related hepatocellular carcinoma (HCC) (9). Similarly, Li et al. found that after adjusting for age, sex, type 2 diabetes, cirrhosis, hepatitis B e antigen, and HBV-DNA, A blood group was associated with a higher risk of HBV-related HCC (10). However, Lu et al. found that ABO blood groups were not associated with HBV-related HCC (11). Huang et al. found that AB blood group was associated with a higher risk of HCC (12).

To date, the association of ABO blood groups and Rh factor with the risk of developing PLC in cirrhotic patients is still unclear. To the best of our knowledge, only one study by Iavarone et al. which retrospectively included 215 cirrhotic patients without HCC and 194 cirrhotic patients with HCC, found that non-O blood group was significantly associated with a higher risk of HCC. However, this association was weak probably due to a limited sample size (13). In this setting, we carried out a cross-sectional study to evaluate the association of ABO blood groups and Rh factor with the presence of PLC in cirrhotic patients.

2 Methods

2.1 Study design

We retrospectively reviewed the medical records of patients with liver cirrhosis who were consecutively admitted to the Department of Gastroenterology of the General Hospital of Northern Theater Command from 1 January 2010 to 30 June 2014. This study was carried out following the rules of the 1975 Declaration of Helsinki and approved by the Medical Ethical Committee of the General Hospital of Northern Theater Command with an approval number [Y (2024) 008]. Patients' written informed consents were waived by the Medical Ethical Committee of the General Hospital of Northern Theater Command due to the retrospective nature of this study.

The exclusion criteria were as follows: (i) repeated admissions of the same patient; (ii) age < 18 years; (iii) patients who did not have sufficient data about ABO blood groups; (iv) patients who had a history or evidence of other non-hepatic malignancy; and (v) patients who did not have imaging-based evidence for a definite diagnosis of liver cirrhosis during their hospitalizations.

2.2 Diagnosis and definitions

Liver cirrhosis was diagnosed based on clinical manifestations, laboratory tests, imaging, liver stiffness measurement, and histopathological examinations, if necessary. PLC was primarily diagnosed by findings from contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) scans with or without a serum alpha-fetoprotein (AFP) level of greater than 400 ng/mL, or histology, if necessary (2, 10).

According to the presence of A and B antigens on the red blood cells (RBC), the ABO blood group includes (i) A blood group characterized as anti-A (+) and anti-B (−); (ii) B blood group as anti-A (−) and anti-B (+); (iii) O blood group as anti-A (−) and anti-B (−); and (iv) AB blood group as anti-A (+) and anti-B (+). According to the presence or absence of D antigen on the RBC, the Rh factor includes (i) Rh (+) blood group characterized as anti-D (+) and (ii) Rh (−) blood group as anti-D (−).

2.3 Data collection

Demographic, clinical, and laboratory data at admissions were collected, including age, gender, smoking, drinking, etiology of cirrhosis (i.e., HBV infection, HCV infection, and alcohol abuse), hypertension, diabetes, family history of liver cirrhosis, ABO blood groups, Rh factor, red blood cells (RBC), hemoglobin (Hb), white blood cell (WBC), platelet count (PLT), total bilirubin (TBIL), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), gamma-glutamyltransferase (GGT), serum creatinine (Scr), blood urea nitrogen (BUN), serum sodium (Na), international normalized ratio (INR), activated partial thromboplastin time (APTT), and AFP. Child–Pugh score and class and Model for End-Stage Liver Disease (MELD) score were also calculated.

2.4 Statistical analyses

All statistical analyses were performed using SPSS version 26.0 statistical software (IBM Corp, Armonk, New York, USA). Continuous variables were expressed as mean ± standard deviation and median (range) and compared using the independent sample *t*-tests for normal distribution or the Mann–Whitney *U*-tests for non-normal distribution. Categorical variables were expressed as frequency (percentage), and their difference between the groups was evaluated using Chi-squared or Fisher's exact tests. Logistic regression analyses were used to explore whether ABO blood groups and Rh factor were significantly associated

Abbreviations: PLC, primary liver cancer; Rh, rhesus; cORs, crude odds ratios; aORs, adjusted odds ratios; 95%CIs, 95% confidence intervals; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; RBC, red blood cell; Hb, hemoglobin; WBC, white blood cell; PLT, platelet count; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AKP, alkaline phosphatase; GGT, gamma-glutamyltransferase; Scr, serum creatinine; BUN, blood urea nitrogen; Na, serum sodium; INR, international normalized ratio; APTT, activated partial thromboplastin time; AFP, alpha-fetoprotein; MELD, Model for End-Stage Liver Disease.

with PLC in cirrhotic patients. Crude odds ratios (cORs) with 95% confidence intervals (CIs) were calculated in univariate analyses. Adjusted odds ratios (aORs) with 95%CIs were calculated after adjusting for gender, age, family history of liver cirrhosis, HBV-DNA, and etiology of cirrhosis. Finally, subgroup analyses were performed to explore the association of ABO blood groups and Rh factor with PLC in patients with different etiologies of liver cirrhosis. Interactions between etiologies of liver cirrhosis and ABO blood groups or Rh factor were tested in subgroup analyses, if appropriate. A two-tailed $p < 0.05$ was considered statistically significant.

3 Results

3.1 Description of overall patients

A total of 1,158 cirrhotic patients without PLC and 240 cirrhotic patients with PLC were included in the study (Figure 1). The mean age of cirrhotic patients without and with PLC was 56.08 and 58.56 years, respectively, and the proportion of male subjects without and with PLC was 66.84% (774/1158) and 79.17% (190/240), respectively.

3.2 Overall comparison between cirrhotic patients without and with PLC

The proportions of male subjects (66.84% vs. 79.17%, $p < 0.001$) and HBV-DNA $\geq 1 \times 10^3$ (22.97% vs. 37.70%, $p = 0.001$), age (56.08 ± 11.82 years vs. 58.56 ± 11.06 years, $p = 0.005$), and AFP level (8.91 ± 39.26 vs. 78.51 ± 138.88, $p < 0.001$) were significantly different between cirrhotic patients without and with PLC. Cirrhotic patients with PLC had a significantly higher prevalence of HBV infection alone (50.00% vs. 30.74%, $p < 0.001$) but a lower prevalence of alcohol abuse alone (12.08% vs. 23.40%, $p < 0.001$) than those without. The proportions of A (28.41% vs. 25.00%, $p = 0.283$), B (32.56% vs. 33.33%, $p = 0.815$), O (28.15% vs. 32.08%, $p = 0.221$), AB (10.88% vs.

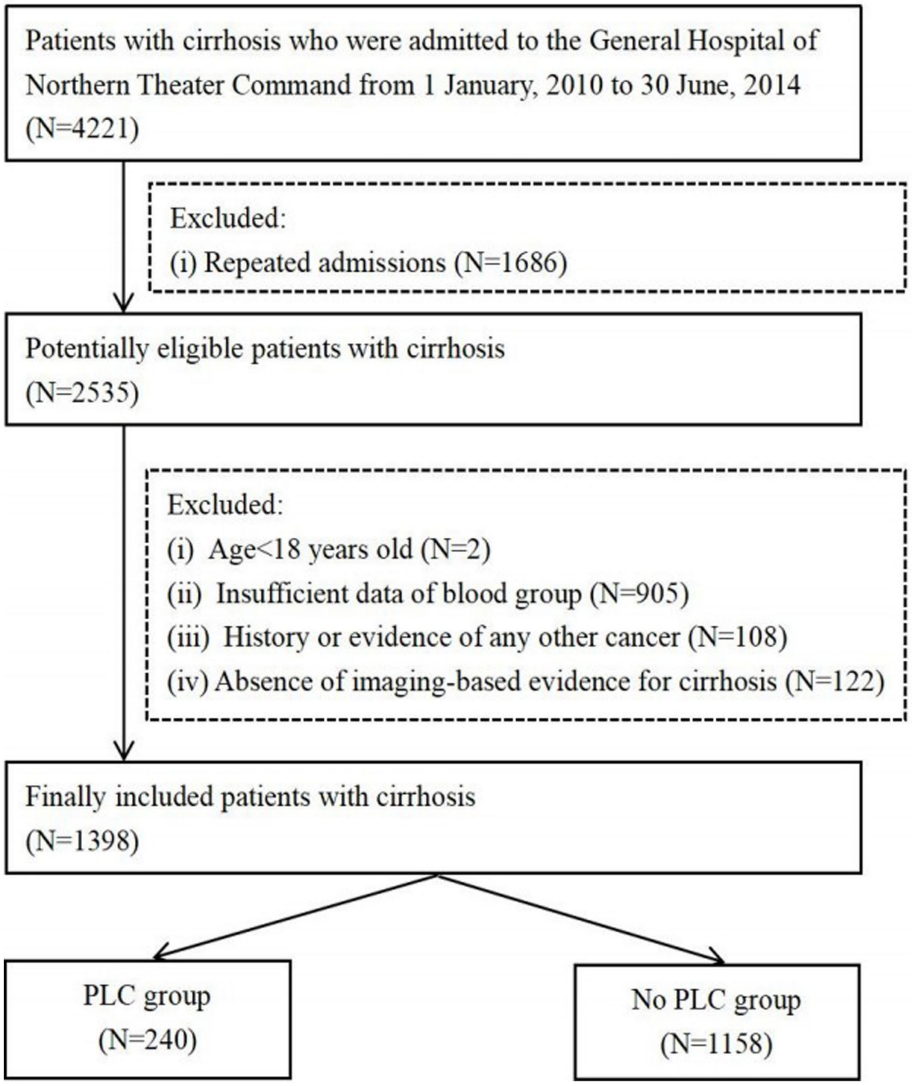

FIGURE 1
Flowchart of patients selection.

9.58%, $p = 0.553$), and Rh (+) (99.30% vs. 98.60%, $p = 0.569$) blood groups were not significantly different between cirrhotic patients without and with PLC (Table 1).

Collectively, ABO blood groups and Rh factor were not associated with PLC in overall patients.

3.3 Logistic regression analyses regarding the association of ABO blood groups and Rh factor with PLC in liver cirrhosis

Univariate logistic regression analyses showed that male subjects (cOR = 1.885, 95%CI = 1.349–2.635, $p < 0.001$), age ≥ 60 years (cOR = 1.452, 95%CI = 1.094–1.927, $p = 0.010$), family history of liver cirrhosis (cOR = 2.461, 95%CI = 1.041–5.818, $p = 0.040$), HBV-DNA ≥ 1×10^3 (cOR = 2.029, 95%CI = 1.334–3.087, $p = 0.001$), HBV infection alone (cOR = 3.150, 95%CI = 2.038–4.868, $p < 0.001$), and HCV infection alone (cOR = 2.721, 95%CI = 1.490–4.967, $p = 0.001$) were significantly associated with PLC in cirrhotic patients (Table 2).

Compared with O blood group, non-O (cOR = 0.829, 95%CI = 0.615–1.119, $p = 0.221$), A (cOR = 0.772, 95%CI = 0.533–1.119, $p = 0.171$), B (cOR = 0.898, 95%CI = 0.635–1.270, $p = 0.544$), and AB (cOR = 0.773, 95%CI = 0.465–1.286, $p = 0.321$) blood groups were not significantly associated with PLC in cirrhotic patients. Multivariate logistic regression analyses also showed that non-O (aOR = 0.763, 95%CI = 0.449–1.298, $p = 0.319$), A (aOR = 0.643, 95%CI = 0.332–1.246, $p = 0.191$), B (aOR = 0.835, 95%CI = 0.453–1.540, $p = 0.564$), and AB (aOR = 0.888, 95%CI = 0.363–2.170, $p = 0.795$) blood groups were not independently associated with PLC in cirrhotic patients (Table 3).

Compared with Rh (−) blood group, Rh (+) blood group (cOR = 0.520, 95%CI = 0.137–1.974, $p = 0.336$) was not significantly associated with PLC in cirrhotic patients. Multivariate logistic regression analysis showed that Rh factor (aOR = 0.239, 95%CI = 0.036–1.571, $p = 0.136$) was not independently associated with PLC in cirrhotic patients (Table 3).

Collectively, ABO blood groups and Rh factor were not significantly associated with PLC in cirrhotic patients.

3.4 Subgroup comparison between cirrhotic patients without and with PLC

3.4.1 HBV infection alone

In the subgroup of patients with HBV infection alone, the proportion of A blood group was significantly higher in cirrhotic patients without PLC than those with PLC (33.99% vs. 24.17%, $p < 0.001$), but the proportions of B, O, AB, and Rh (+) blood groups were not significantly different between cirrhotic patients without and with PLC (Table 4).

Compared with O blood group, A blood group (cOR = 0.536, 95%CI = 0.307–0.936, $p = 0.028$), rather than non-O, B, and AB blood groups, was significantly associated with a lower risk of PLC in cirrhotic patients with HBV infection alone (Figure 2). However, multivariate logistic regression analyses showed that A blood group was not independently associated with PLC in cirrhotic patients with HBV infection alone (Figure 3).

Compared with Rh (−) blood group, Rh (+) blood group (cOR = 0.657, 95%CI = 0.059–7.313, $p = 0.732$) was not significantly associated with PLC in cirrhotic patients with HBV infection alone (Figure 2). Multivariate logistic regression analysis showed that Rh factor (aOR = 0.209, 95%CI = 0.011–4.081, $p = 0.302$) was not independently associated with PLC in cirrhotic patients with HBV infection alone (Figure 3).

3.4.2 HCV infection alone

In the subgroup of patients with HCV infection alone, the proportions of A, B, O, AB, and Rh (+) blood groups were not significantly different between cirrhotic patients without and with PLC (Table 4).

Compared with O blood group, non-O, A, B, and AB blood groups were not significantly associated with PLC in cirrhotic patients with HCV infection alone (Figure 2). Multivariate logistic regression analyses showed that non-O, A, B, and AB blood groups were not independently associated with PLC in cirrhotic patients with HCV infection alone (Figure 3).

3.4.3 Alcohol abuse alone

In the subgroup of patients with alcohol abuse alone, the proportions of A, B, O, AB, and Rh (+) blood groups were not significantly different between cirrhotic patients without and with PLC (Table 4).

Compared with O blood group, non-O, A, B, and AB blood groups were not significantly associated with PLC in cirrhotic patients with alcohol abuse alone (Figure 2). Multivariate logistic regression analyses showed that non-O, A, B, and AB blood groups were not independently associated with PLC in cirrhotic patients with alcohol abuse alone (Figure 3).

Compared with Rh (−) blood group, Rh (+) blood group (OR = 0.175, 95%CI = 0.015–2.011, $p = 0.162$) was not significantly associated with PLC in cirrhotic patients with alcohol abuse alone (Figure 2). Multivariate logistic regression analysis also showed that Rh factor (aOR = 0.188, 95%CI = 0.016–2.204, $p = 0.183$) was not independently associated with PLC in cirrhotic patients with alcohol abuse alone (Figure 3).

3.4.4 Interaction in subgroup analyses

There was no significant interaction between the etiologies of liver cirrhosis and ABO blood groups or Rh factor (Figures 2, 3).

Collectively, ABO blood groups and Rh factor were not independently associated with PLC in patients with different etiologies of liver cirrhosis.

4 Discussion

Our study did not demonstrate any significant association of ABO blood groups and Rh factor with the risk of PLC in cirrhotic patients. Some possible explanations for this finding are as follows: First, the development of PLC is largely influenced by acquired factors but less affected by inherited factors. The majority of our patients had hepatitis B or C virus infection (41.34%) and alcohol abuse (21.46%) as the underlying etiologies of liver diseases, which are also the leading causes of PLC. By comparison, ABO blood groups and Rh factor are inherited characteristics of human populations (14). Second, the development of PLC in cirrhotic patients is largely determined by the regulation of microRNAs, which are a series of small, single-stranded RNAs with approximately 22 nucleotides (15–19) and do not encode the proteins but repress the expression of their target mRNAs on transcriptional

TABLE 1 Comparison between cirrhotic patients without and with PLC.

Variables	Cirrhosis without PLC		Cirrhosis with PLC		*p*-value
	No. Pts	Median (range), Mean ± SD or Frequency (percentage)	No. Pts	Median (range), Mean ± SD or Frequency (percentage)	
Demographics					
Age (years)	1,158	55.66 (21.19–95.13); 56.08 ± 11.82	240	57.16 (23.80–88.29); 58.56 ± 11.06	**0.005**
Male	1,158	774 (66.84%)	240	190 (79.17%)	**<0.001**
Smoking (%)	850	276 (32.47%)	191	71 (37.17%)	0.213
Drinking (%)	856	345 (40.30%)	192	77 (40.10%)	0.959
Family history of liver cirrhosis (%)	1,158	16 (1.40%)	240	8 (3.33%)	0.065
Hypertension (%)	1,158	160 (13.82%)	240	36 (15.00%)	0.631
Diabetes (%)	1,158	212 (18.31%)	240	43 (17.92%)	0.887
Etiology of liver cirrhosis					
HBV infection alone (%)	1,158	356 (30.74%)	240	120 (50.00%)	**<0.001**
HCV infection alone (%)	1,158	79 (6.82%)	240	23 (9.58%)	0.134
Alcohol abuse alone (%)	1,158	271 (23.40%)	240	29 (12.08%)	**<0.001**
ABO blood groups (%)					
O (%)	1,158	326 (28.15%)	240	77 (32.08%)	0.221
A (%)	1,158	329 (28.41%)	240	60 (25.00%)	0.283
B (%)	1,158	377 (32.56%)	240	80 (33.33%)	0.815
AB (%)	1,158	126 (10.88%)	240	23 (9.58%)	0.553
Rh (+) (%)	1,091	1,083 (99.30%)	214	211 (98.60%)	0.569
Laboratory parameters					
HBV-DNA $\geq 1 \times 10^3$ (%)	518	119 (22.97%)	122	46 (37.70%)	**0.001**
RBC (10^{12}/L)	1,151	3.04 (0.93–6.78); 3.08 ± 0.87	235	3.60 (1.28–5.75); 3.52 ± 0.87	**<0.001**
Hb (g/L)	1,151	89.00 (27.00–218.00); 92.43 ± 30.22	235	113.00 (31.00–169.00); 110.49 ± 28.05	**<0.001**
WBC (10^9/L)	1,151	4.20 (0.30–46.10); 5.35 ± 4.20	235	5.00 (1.10–38.00); 6.09 ± 4.08	**<0.001**
PLT (10^9/L)	1,151	74.00 (5.00–592.00); 94.34 ± 71.45	235	90.00 (23.00–437.00); 109.49 ± 66.96	**<0.001**
TBIL (μmol/L)	1,146	21.80 (2.00–809.80); 43.03 ± 71.11	234	23.55 (6.30–491.90); 47.99 ± 72.16	0.315
ALB (g/L)	1,125	31.90 (0.40–52.80); 31.91 ± 7.18	235	34.00 (14.00–48.90); 33.29 ± 6.90	**0.007**
AST (U/L)	1,145	36.00 (8.00–1487.00); 60.20 ± 113.38	234	57.00 (14.00–663.00); 85.33 ± 90.49	**<0.001**
ALT (U/L)	1,145	26.00 (3.00–1335.00); 40.96 ± 73.05	234	39.00 (9.00–762.00); 57.91 ± 71.60	**<0.001**
AKP (U/L)	1,143	82.00 (7.05–969.00); 107.94 ± 88.10	234	111.00 (30.00–769.00); 142.58 ± 107.40	**<0.001**
GGT (U/L)	1,143	44.00 (5.00–4562.00); 105.91 ± 209.76	234	100.00 (8.00–1091.00); 146.39 ± 148.37	**<0.001**
Scr (umol/L)	1,130	60.95 (20.00–1069.00); 82.02 ± 98.06	230	60.30 (25.00–355.00); 72.22 ± 42.05	0.559
BUN (mmol/L)	1,129	5.92 (1.63–61.88); 7.98 ± 6.88	230	5.75 (2.06–41.58); 7.16 ± 4.62	0.371
Na (mmol/L)	1,144	139.00 (116.40–160.80); 138.43 ± 4.70	233	138.60 (112.10–147.90); 137.72 ± 5.08	0.107
INR	1,127	1.26 (0.77–5.94); 1.39 ± 0.53	232	1.16 (0.84–4.33); 1.28 ± 0.46	**<0.001**
APTT (s)	1,125	42.00 (21.90–168.00); 43.47 ± 9.79	233	41.60 (28.20–105.30); 42.37 ± 8.79	0.064
AFP (IU/ml)	751	2.96 (0.28–802.60); 8.91 ± 39.26	138	9.79 (0.23–606.90); 78.51 ± 138.88	**<0.001**
Child–Pugh score	1,090	7.00 (5.00–15.00); 7.68 ± 2.21	224	7.00 (5.00–14.00); 7.35 ± 2.20	**0.028**
Child–Pugh class					
A (%)	1,090	397 (36.42%)	224	96 (42.86%)	0.070
B (%)	1,090	465 (42.66%)	224	88 (39.29%)	0.351
C (%)	1,090	228 (20.92%)	224	40 (17.86%)	0.301
MELD score	1,105	9.54 (6.43–40.00); 12.41 ± 7.57	225	8.19 (6.43–31.38); 10.05 ± 5.00	**<0.001**

No. Pts, number of patients; PLC, primary liver cancer; SD, standard deviation; HBV, hepatitis B virus; HCV, hepatitis C virus; RBC, red blood cell; Hb, hemoglobin; WBC, white blood cell; PLT, platelet count; TBIL, total bilirubin; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AKP, alkaline phosphatase; GGT, gamma-glutamyltransferase; Scr, serum creatinine; BUN, blood urea nitrogen; Na, serum sodium; INR, international normalized ratio; APTT, activated partial thromboplastin time; AFP, alpha-fetoprotein; MELD, Model of End-Stage Liver Disease. Notes to bold values: There were significant differences between the two groups.

TABLE 2 Univariate logistic regression analyses for risk factors of PLC.

Variables	Univariate analysis	
	Crude OR (95% CI)	*p*-value
Sex		**<0.001**
Female	1	
Male	1.885 (1.349–2.635)	
Age		**0.010**
<60	1	
≥60	1.452 (1.094–1.927)	
Family history of liver cirrhosis		**0.040**
No	1	
Yes	2.461 (1.041–5.818)	
History of smoking		0.213
No	1	
Yes	1.230 (0.888–1.706)	
History of drinking		0.959
No	1	
Yes	0.992 (0.721–1.365)	
Diabetes		0.887
No	1	
Yes	0.974 (0.678–1.399)	
Hypertension		0.631
No	1	
Yes	1.101 (0.744–1.628)	
HBV-DNA		**0.001**
$<1 \times 10^3$	1	
$\geq 1 \times 10^3$	2.029 (1.334–3.087)	
Etiology of liver cirrhosis		
Alcohol abuse alone (%)	1	
HBV infection alone (%)	3.150 (2.038–4.868)	**<0.001**
HCV infection alone (%)	2.721 (1.490–4.967)	**0.001**
Child–Pugh class		
A (%)	1	
B (%)	0.783 (0.569–1.076)	0.132
C (%)	0.726 (0.485–1.086)	0.119
Laboratory parameters		
RBC (10^{12}/L)	1.791 (1.519–2.113)	**<0.001**
Hb (g/L)	1.020 (1.015–1.025)	**<0.001**
WBC (10^9/L)	1.038 (1.007–1.069)	**0.015**
PLT (10^9/L)	1.003 (1.001–1.004)	**0.003**
TBIL (μmol/L)	1.001 (0.999–1.003)	0.334
ALB (g/L)	1.028 (1.007–1.049)	**0.007**
ALT (U/L)	1.002 (1.001–1.004)	**0.005**
AST (U/L)	1.002 (1.000–1.003)	**0.004**
Scr (umol/L)	0.998 (0.996–1.001)	0.150
BUN (mmol/L)	0.977 (0.952–1.003)	0.085
Na (mmol/L)	0.970 (0.943–0.999)	**0.040**
INR	0.553 (0.376–0.815)	**0.003**
APTT (s)	0.986 (0.970–1.003)	0.111
Child–Pugh score	0.933 (0.872–0.998)	**0.045**
MELD score	0.940 (0.913–0.967)	**<0.001**

PLC, primary liver cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; RBC, red blood cell; Hb, hemoglobin; WBC, white blood cell; PLT, platelet count; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; BUN, blood urea nitrogen; Na, serum sodium; INR, international normalized ratio; APTT, activated partial thromboplastin time; MELD, Model of End-Stage Liver Disease. Notes to bold values: There were significant differences between the two groups.

TABLE 3 Univariate and multivariate logistic regression analyses of ABO blood groups and Rh factor in cirrhotic patients with PLC.

Variables	Univariate analysis		Multivariate analysis**	
	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
ABO blood groups				
O	1			
Non-O	0.829 (0.615–1.119)	0.221	0.763 (0.449–1.298)	0.319
A	0.772 (0.533–1.119)	0.171	0.643 (0.332–1.246)	0.191
B	0.898 (0.635–1.270)	0.544	0.835 (0.453–1.540)	0.564
AB	0.773 (0.465–1.286)	0.321	0.888 (0.363–2.170)	0.795
Rh factor				
Rh (−)	1			
Rh (+)	0.520 (0.137–1.974)	0.336	0.239 (0.036–1.571)	0.136

**Adjusted for gender, age, family history of liver cirrhosis, HBV-DNA, and etiology of liver cirrhosis. PLC, primary liver cancer. Notes to bold values: There were significant differences between the two groups.

TABLE 4 Comparison of the proportions of ABO blood groups and Rh factor in subgroup analyses between cirrhotic patients without and with PLC.

Subgroups	Cirrhosis without PLC		Cirrhosis with PLC		*p*-value
	No. Pts	Frequency (percentage)	No. Pts	Frequency (percentage)	
HBV infection alone					
O	356	85 (23.88%)	120	38 (31.67%)	0.092
A	356	121 (33.99%)	120	29 (24.17%)	**<0.001**
B	356	110 (30.90%)	120	40 (33.33%)	0.620
AB	356	40 (11.24%)	120	13 (10.83%)	0.903
Rh (+)	337	335 (99.41%)	111	110 (99.10%)	0.575
HCV infection alone					
O	79	25 (31.65%)	23	8 (34.78%)	0.777
A	79	18 (22.78%)	23	7 (30.43%)	0.453
B	79	27 (34.18%)	23	5 (21.74%)	0.258
AB	79	9 (11.39%)	23	3 (13.04%)	1.000
Rh (+)	73	72 (98.63%)	21	21 (100%)	1.000
Alcohol abuse alone					
O	271	83 (30.63%)	29	9 (31.03%)	0.964
A	271	72 (26.57%)	29	6 (20.69%)	0.493
B	271	89 (32.84%)	29	12 (41.38%)	0.355
AB	271	27 (9.96%)	29	2 (6.90%)	0.841
Rh (+)	253	251 (99.21%)	23	22 (95.65%)	0.231

No. Pts, number of patients; PLC, primary liver cancer; HBV, hepatitis B virus; HCV, hepatitis C virus. Notes to bold values: There were significant differences between the two groups.

and translational levels (20). In cirrhotic patients, multiple signaling pathways and gene expressions can be affected by upgrading the microRNA-21 level and downgrading the microRNA-122, microRNA-29, microRNA-223, and microRNA-193 levels, thereby decreasing cell apoptosis and increasing tumor cell proliferation, invasion, and migration, eventually promoting the development of PLC (21). By comparison, blood groups are differentiated by the presence of A and B antigens on the RBC, which are glycoproteins or glycolipids distributed on the RBC membrane (21) and the products of the gene on chromosome 9q34 (22). Notably, the microRNA level cannot be affected when encoding A and B antigens. Third, the impact of ABO blood groups on PLC may be diluted or even masked by more dominant risk factors, such as hepatitis. Indeed, our previous meta-analysis found that the proportion of O blood group in patients with HCC was significantly lower than that in healthy subjects, but the proportions of ABO blood groups were not significantly different between patients with HCC and hepatitis (23). A case–control study by Shim et al. found that A blood group was associated with a higher risk of PLC in subjects without hepatitis, but ABO blood groups were not significantly associated with PLC in subjects with hepatitis (24). Thus, it can be inferred that ABO blood groups may be associated with PLC in healthy people, but not in patients with hepatitis. Notably, our patients mostly had viral hepatitis, so we did not find any association of ABO blood groups with PLC.

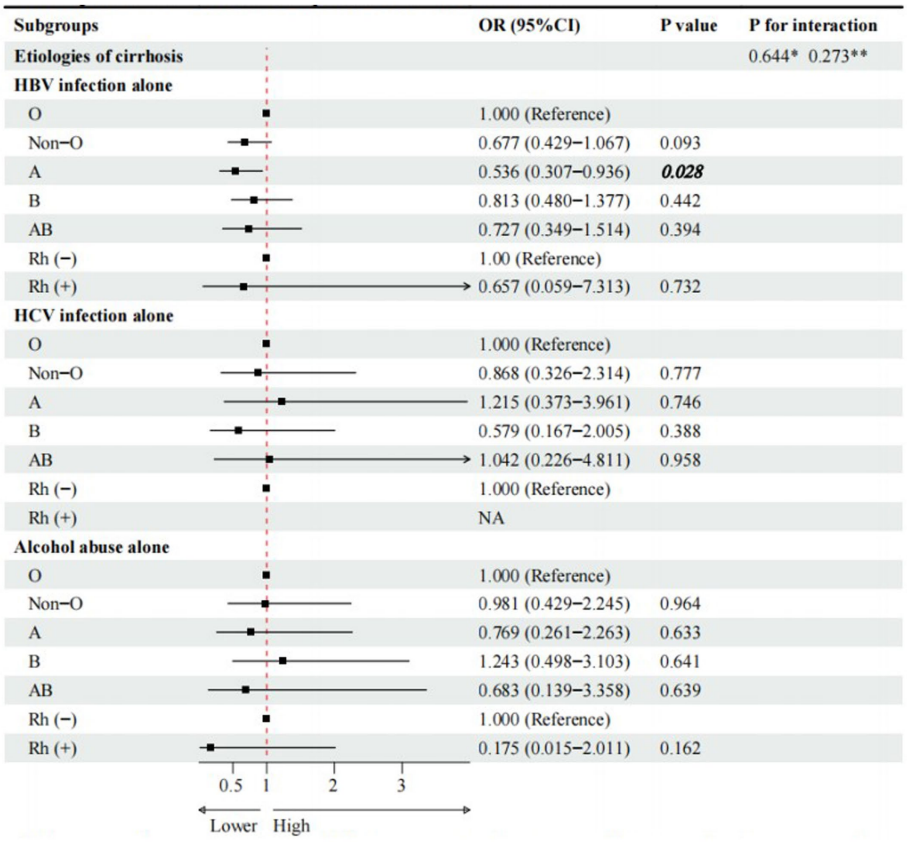

FIGURE 2
Univariate logistic regression analyses for subgroup analyses of cirrhotic patients with PLC. * Interaction among different etiologies of liver cirrhosis with ABO blood groups. **Interaction among different etiologies of liver cirrhosis with Rh factor. Notes to bold values: There were significant differences between the two groups.

Another finding of our study was that A blood group was a protective factor for PLC in cirrhotic patients with HBV infection alone in univariate logistic regression analyses. However, it should be acknowledged that after adjusting for gender, age, family history of liver cirrhosis, and HBV-DNA, A blood group was not independently associated with PLC in cirrhotic patients with HBV infection alone, which is almost consistent with previous study (11). Therefore, the protective effect of A blood group on PLC, as shown in the univariate analyses, may be caused by confounding factors. Further studies are needed to investigate the association between ABO blood groups and PLC in different settings.

Our study has several advantages as follows. First, to the best of our knowledge, this should be the first study to explore the association of ABO blood groups and Rh factor with the presence of PLC in cirrhotic patients from Liaoning province, China. Second, the selection of eligible patients in our study was more rigorous and reasonable. All subjects included in our study had a diagnosis of cirrhosis. As known, PLC often develops in the setting of cirrhosis. Thus, our data should be more comparable. Third, imaging-based evidence for a definite diagnosis of liver cirrhosis can be obtained in all eligible patients. Thus, our findings should be more accurate and convincing. Fourth, we had a relatively large sample size. Fifth, we adjusted for confounding factors and performed subgroup analyses according to the etiology of liver cirrhosis.

The limitations of our study should not be ignored. First, this was a retrospective cross-sectional study at a single center. Thus, the cause–effect association of ABO blood groups and Rh factor with the development of PLC in cirrhosis could not be clarified. In addition, selection and information bias were inevitable, which may affect the external validity of our study and lead to inaccurate results. Second, most eligible patients included in our study lived in Liaoning province, China. Hence, the findings might be inappropriate to the population from different regions. Third, we did not subdivide the genotypes of the ABO blood groups. In detail, A blood group is composed of AA genotype and AO genotype. B blood group is composed of BB genotype and BO genotype. Therefore, we could not confirm any association of specific ABO genotypes with the risk of PLC in cirrhotic patients.

In conclusion, ABO blood groups and Rh factor may not be associated with the presence of PLC in cirrhotic patients. More large-scale and high-quality prospective studies, multicenter trials, or investigations into the biological mechanisms linking ABO blood groups and Rh factor with PLC are needed to explore the association of ABO blood groups and Rh factor with the risk of PLC among healthy subjects and patients with chronic liver diseases.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors. The datasets presented in this article are not readily available because our data is not open to the public. Requests to access the datasets should be directed to Xingshun Qi, xingshunqi@126.com.

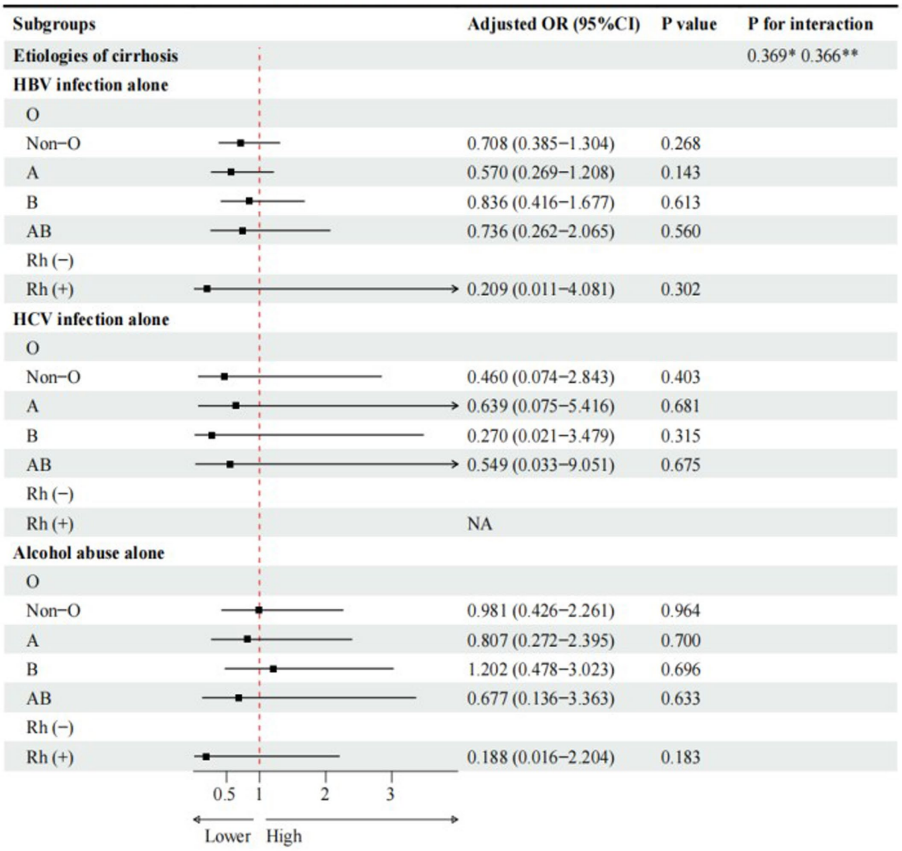

FIGURE 3
Multivariate logistic regression analyses for subgroup analyses of cirrhotic patients with PLC. Adjusted for gender, age, family history of liver cirrhosis, HBV-DNA. * Interaction among different etiologies of liver cirrhosis with ABO blood groups. **Interaction among different etiologies of liver cirrhosis with Rh factor.

Ethics statement

The studies involving humans were approved by the Medical Ethical Committee of General Hospital of Northern Theater Command. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because patients' written informed consents were waived by the Medical Ethical Committee of General Hospital of Northern Theater Command due to the retrospective nature of this study.

Author contributions

LD: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Investigation. YY: Writing – original draft, Methodology, Investigation. HL: Software, Data curation, Writing – original draft. DS: Writing – original draft, Data curation. DW: Writing – review & editing, Investigation, Data curation. DZ: Writing – review & editing, Investigation, Data curation. XQ: Writing – review & editing, Supervision, Project administration, Conceptualization, Investigation.

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Conflict of 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.

Publisher's note

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Hepatic encephalopathy and spontaneous bacterial peritonitis are associated with increased liver-related readmissions in cirrhosis

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Introduction: Liver disease remains a significant global health concern. In China, the number of patients with liver cirrhosis is estimated to reach 7 million. In addition to the high risk of death, cirrhosis leads to several severe complications. Patients with cirrhosis have significantly longer hospital stays and higher total hospital costs than those without cirrhosis. We aimed to investigate the predictors of readmission among patients with cirrhosis in China.

Materials and methods: We conducted a retrospective study to evaluate adult patients with cirrhosis. Data on various sociodemographic, clinical, and hospitalization characteristics were collected. We defined the primary endpoint as the first liver-related readmission occurring within 30–90 days of initial hospitalization. Adult patients with cirrhosis admitted to our hospital between January 2009 and December 2022 were included. Differences between groups were analyzed using Student's t-test and chi-square test. Logistic and multiple linear regression analyses were performed to identify predictors associated with readmission and the length of the first hospitalization.

Results: In total, 1,285 patients were diagnosed with cirrhosis. Among these patients, 767 (59.7%) were males, and the mean age was 58.9 ± 12.3 years. Seventy-two (5.6%) and 154 (12.0%) patients were readmitted within 30 and 90 days, respectively. Compared with those who were not readmitted, patients readmitted at 30-day and 90-day had a higher proportion of males, ascites, spontaneous bacterial peritonitis, electrolyte abnormalities, higher Child-Pugh–Turcotte scores, longer initial hospital stays, and higher initial hospitalization costs. Logistic regression analysis indicated that hepatic encephalopathy, spontaneous bacterial peritonitis, diabetes, and ascites were predictors of 30- and 90-day readmission. Hypertension and spontaneous bacterial peritonitis were significant predictors of the length of the first hospitalization.

Conclusion: Patients with cirrhosis presenting with hepatic encephalopathy, ascites, and spontaneous bacterial peritonitis may have a higher risk of rehospitalization.

KEYWORDS

liver cirrhosis, readmission, hepatic encephalopathy, spontaneous bacterial peritonitis, hypertension

1 Introduction

Liver disease remains a significant global health concern, resulting in approximately 2 million deaths annually worldwide, with 1 million fatalities attributed to cirrhosis complications. Cirrhosis is the 11th most common cause of death globally (1). In 2017, cirrhosis led to over 1.32 million deaths, comprising 2.4% of all global deaths (2). In China, the number of patients suffering from liver cirrhosis is estimated to approach 7 million (3), in whom approximately 460,000 new cases of hepatocellular carcinoma (HCC) are reported each year (4). Patients with compensated cirrhosis have a 4.7 times higher risk of death than the general population, whereas those with decompensated cirrhosis have a 9.7 times higher risk (5). Besides the high risk of death, cirrhosis leads to several severe complications, including ascites, variceal hemorrhage, hepatic encephalopathy (HE), HCC, spontaneous bacterial peritonitis (SBP), and malnutrition. These complications can significantly affect the patients' quality of life, prevent them from working due to worsened physical and mental health, and impose substantial financial burdens (5, 6). Compared to individuals without cirrhosis, patients with cirrhosis experience significantly longer hospital stays and higher total hospital charges (7). Additionally, those with comorbid cirrhosis face a higher likelihood of 30-day and 90-day readmissions than patients without cirrhosis (7).

Patients with advanced liver disease have high readmission rates (8). Previous studies estimated the 30-day readmission rate in patients with cirrhosis to be 26% (9). Similarly, the readmission rate within 1 year was reported to be 28.7% in China (10). A study conducted in Texas showed that patients with chronic liver disease (25%) had a higher 30-day readmission rate than those with congestive heart failure (21.9%) or chronic obstructive pulmonary disease (20.6%) (11). Readmission of inpatients with cirrhosis is associated with a deteriorated quality of life and a higher risk of death (12). These readmissions not only pose challenges to patient health but also impose an increased financial burden (13). In the United States, the cost of cirrhosis-related hospitalizations doubled from $4.8 billion to $9.8 billion between 2001 and 2011 (14).

Numerous factors are associated with readmission in patients with cirrhosis, including socioeconomic characteristics, cirrhosis type, hepatorenal syndrome, ascites, variceal hemorrhage, HCC, Charlson Comorbidity Index, and HE (13, 15). In particular, HE has been identified as a significant predictor of 30-day and 90-day readmission in patients with cirrhosis, along with the presence of >3 cirrhotic complications (15). These structural changes have led to the pathogenesis of cirrhosis in recent years (16) The application of antivirals for hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as large-scale neonatal HBV vaccination, has reduced the prevalence of cirrhosis related to viral hepatitis (14, 17, 18). To date, non-alcoholic steatohepatitis (NASH) and alcohol-related liver disease are the most common causes of liver cirrhosis (19–21). Therefore, further research is needed to identify the factors that influence readmitted hospital admissions in patients with cirrhosis, to treat patients, and to avoid the deterioration of these conditions early. We conducted a retrospective study to gain insight into the predictors influencing readmission in patients with cirrhosis in China.

2 Materials and methods

2.1 Data source

We conducted a retrospective study at a single center to evaluate adult patients with cirrhosis. The study period spanned from January 2009 to December 2022. We identified patients through our hospital's electronic medical records using admission diagnoses of cirrhosis with the International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM) codes K74.100 and K74.607. We excluded patients with incomplete information, those who were lost to follow-up, or those who died during the index hospitalization. The study was conducted in accordance with the ethical guidelines outlined in the 1975 Declaration of Helsinki (6th revision, 2008) and was approved by the Ethics Committee of Peking University People's Hospital (No. 2023PHB214-001). Given the retrospective nature of the study, the requirement for informed consent was waived, and none of the enrolled patients were asked to provide informed consent.

2.2 Participants

Adult patients with cirrhosis who were admitted to our hospital between January 2009 and December 2022 were included in this study.

2.3 Main measures

We collected a comprehensive range of sociodemographic, clinical, and hospitalization characteristics, including sex, age, type of medical insurance (Chinese resident medical insurance and Chinese worker medical insurance), and baseline liver disease etiology (alcohol-related liver disease, viral hepatitis, or other causes, such as non-alcoholic steatohepatitis, drug-induced liver injury, or autoimmune liver disease). Comorbidities were documented, including hypertension (I10. ×00 × 002), diabetes mellitus (E14.900 × 001), and chronic kidney disease (CKD) (N18.900 × 005). We also recorded liver disease-related complications, such as HCC (C22.70D), HE (K72.90B), and ascites (R18. ×00), variceal bleeding (K92.201), SBP (K65.016), hepatic hydrothorax (J94.80D), and electrolyte disturbances (E87.800 × 011, E87.600, E87.500, E87.102, and E87.001). In addition, we documented the Model for End-Stage Liver Disease (MELD) and Child-Pugh–Turcotte scores at the time of the patient's first discharge.

Alcoholic liver disease was diagnosed when alcohol consumption was ≥40 g/day in males and ≥ 20 g/day in females, with a history of alcohol intake spanning at least 5 years (22). Liver diseases other than alcoholic liver disease or viral hepatitis were identified based on admission and discharge diagnoses, with only the first occurrence of

each diagnosis recorded. Laboratory data were retrieved from the hospital's clinical data center.

The MELD score was calculated using parameters such as total bilirubin level, creatinine level, international normalized ratio (INR), and history of cholestatic liver disease. The Child-Pugh–Turcotte score was also calculated, and patients were categorized into three groups: A, good hepatic function; B, moderately impaired hepatic function; and C, advanced hepatic dysfunction, based on five clinical and laboratory criteria: serum bilirubin, serum albumin, ascites, neurological disorder, and clinical nutrition status.

2.4 Hospitalization characteristics

The recorded hospitalization characteristics included cirrhosis complications observed during the first admission and readmission. These complications included volume-related issues such as ascites (R18. × 00), hepatic hydrothorax (J94.80D), edema (R60.900), SBP (K65.016), variceal bleeding (K92.201), HCC (C22.70D), HE (K72.90B), liver function deterioration, infections, or other related factors.

Liver function deterioration was diagnosed based on at least one of the following criteria (23, 24): an increase in Child-Pugh score by 2 points or more from baseline; total bilirubin (TBil) levels ≥51 μmol/L or an increase in TBil levels from baseline of ≥34.2 μmol/L; and any increase in prothrombin time (PT) from baseline of ≥3 s. Infections were diagnosed according to international and local guidelines. Patients may have had multiple liver-related reasons for admission, and the major reasons for each admission were recorded. Furthermore, we collected data on the cost of the initial admission and the length of stay for the first hospitalization, calculated from admission to discharge.

2.5 Study outcomes

We defined the primary endpoint as the first liver-related readmission occurring within 30–90 days of initial hospitalization. To capture episodes of hospitalization at other hospitals, we contacted patients who had liver-related readmissions to any hospital since their first hospitalization. Liver-related readmission was defined as previously described. All other readmissions were excluded from the analysis. If a patient had more than one readmission within 30 days, only the first readmission was considered for the analysis. The secondary endpoint was the length of hospitalization at the time of admission.

We collected comprehensive information on readmissions by accessing the electronic medical records of our hospital, including medical histories, physical examinations, daily notes, laboratory results, and discharge summaries. To track hospitalizations at other facilities, we contacted patients with liver-related readmissions via telephone or conducted in-person interviews during subsequent visits to our outpatient clinic or inpatient department.

2.6 Statistical analysis

The normality of the data was evaluated using the Kolmogorov–Smirnov test. Mean ± standard deviation (SD) was used to present as continuous variables were normally distributed. Categorical variables are presented as numbers (%). Differences between groups were analyzed using Student's t-test for variables such as age, MELD score, cost of admission, and length of stay. The chi-square test was used to analyze variables such as insurance, baseline liver disease, comorbidities, complications, treatment, and cause of readmission. Logistic regression analysis using a stepwise selection approach was performed to identify predictors associated with readmission, whereas multiple linear regression analysis was used to identify predictors associated with the length of the first hospitalization. For logistic model diagnostics, we employed the Hosmer-Lemeshow goodness-of-fit test to evaluate the calibration of our logistic regression models. A p-value <0.05 was considered statistically significant. All data analyses were conducted using SPSS version 23.0 (IBM Corp, Armonk, NY, USA).

3 Results

3.1 Baseline characteristics of patients with cirrhosis

We enrolled 1,285 patients who were admitted with cirrhosis. Their baseline characteristics are shown in Table 1. Within 30 days, 72 (5.6%) patients were readmitted, and within 90 days, the number increased to 154 (12.0%) patients. Among the patients, 767 (59.7%) were male, and the mean age was 58.9 ± 12.3 years. A total of 117 (9.1%) patients had no insurance coverage. Alcoholic cirrhosis was observed in 375 (29.2%) patients. On admission, 209 (16.3%), 1,192 (92.8%), and 88 (6.8%) patients presented with HE, ascites, and esophagogastric variceal bleeding, respectively. The mean MELD score was 9.9 ± 5.7. Regarding the Child-Pugh–Turcotte score, 726 (59.9%) and 219 (18.1%) patients were classified as Grade B and Grade C, respectively.

Considering 30-day and 90-day readmission cases This subgroup consisted of a higher proportion of males (30-day: 52 [72.2%] vs. 715 [58.9%], $p = 0.016$; 90-day: 104 [67.5%] vs. 663 [58.6%], $p = 0.020$) and individuals with alcoholic cirrhosis (30-day: 35 [48.6%] vs. 340 [28%], $p < 0.001$; 90-day: 64 [41.6%] vs. 311 [27.5%], $p < 0.001$) compared to those who did not experience readmission within the 30-day or 90-day timeframe. Patients admitted for 90 days had a lower proportion of HBV infections (45 [29.2%] vs. 433 [38.3%], $p = 0.016$). Furthermore, among the readmitted patients, a higher prevalence of HE (30-day: 27 [37.5%] vs. 182 [15.0%], $p < 0.001$; 90 day: 51 [33.1%] vs. 158 [14%], $p < 0.001$), ascites (30 day: 72 [100%] vs. 1,120 [92.3%], $p = 0.004$; 90-day: 152 [98.7%] vs. 1,040 [92.0%], $p < 0.001$), SBP (30-day: 29 [40.3%] vs. 168 [13.8%], $p < 0.001$; 90-day: 49 [31.8%] vs. 148 [13.1%], $p < 0.001$), and electrolyte abnormalities (30-day: 26 [36.1%] vs. 577 [47.6%], $p < 0.001$; 90-day:61 [39.6%] vs. 542 [47.9%], $p < 0.001$) was observed. Notably, readmitted patients had significantly higher Child-Pugh Turcotte scores than those who were not readmitted (30-day, $p < 0.001$, 90-day, $p < 0.001$).

3.2 Hospitalization characteristics

The major causes of first admission were volume-related (568, 44.2%), liver function deterioration (285, 22.2%), HE (101, 7.9%),

TABLE 1 Baseline characteristics of included patients.

Characteristics	All *n* = 1,285	30-day readmission			90-day readmission		
		Not readmitted *n* = 1,213	Readmitted *n* = 72	*p*-value	Not readmitted *n* = 1,131	Readmitted *n* = 154	*p*-value
Age (years), mean ± SD	58.9 ± 12.3	58.9 ± 12.4	59.2 ± 11.0	0.802	58.7 ± 12.5	60.3 ± 10.9	0.126
Male, *n* (%)	767 (59.7)	715 (58.9)	52 (72.2)	0.016	663 (58.6)	104 (67.5)	0.020
Insurance, *n* (%)				0.196			0.334
Any insurance	1,168 (90.9)	1,100 (90.7)	68 (94.4)		1,026 (90.7)	142 (92.2)	
No insurance	117 (9.1)	113 (9.3)	4 (5.6)		105 (9.3)	12 (7.8)	
Baseline liver disease, *n* (%)							
Alcohol	375 (29.2)	340 (28.0)	35 (48.6)	< 0.001	311 (27.5)	64 (41.6)	< 0.001
HBV infection	478 (37.2)	458 (37.8)	20 (27.8)	0.103	433 (38.3)	45 (29.2)	0.033
HCV infection	108 (8.4)	98 (8.1)	10 (13.9)	0.120	89 (7.9)	19 (12.3)	0.064
Other[a]	441 (34.3)	422 (34.8)	19 (26.4)	0.090	396 (35.0)	45 (29.2)	0.091
Co-morbidities, *n* (%)							
Hypertension	429 (33.4)	397 (32.7)	32 (44.4)	0.029	362 (32.0)	67 (43.5)	0.003
Diabetes	340 (26.5)	313 (25.8)	27 (37.5)	0.023	283 (25.0)	57 (37.0)	0.001
Chronic kidney disease	130 (10.1)	118 (9.7)	12 (16.7)	0.052	110 (9.7)	20 (13.0)	0.133
Complications, *n* (%)							
Hepatocellular carcinoma	235 (18.3)	220 (18.1)	15 (20.8)	0.329	200 (17.7)	35 (22.7)	0.082
Hepatic encephalopathy	209 (16.3)	182 (15.0)	27 (37.5)	< 0.001	158 (14.0)	51 (33.1)	< 0.001
Ascites	1,192 (92.8)	1,120 (92.3)	72 (100.0)	0.004	1,040 (92.0)	152 (98.7)	< 0.001
Variceal bleeding	88 (6.8)	83 (6.8)	5 (6.9)	0.558	77 (6.8)	11 (7.1)	0.491
Spontaneous bacterial peritonitis	197 (15.3)	168 (13.8)	29 (40.3)	< 0.001	148 (13.1)	49 (31.8)	< 0.001
Hepatic hydrothorax	116 (9.0)	113 (9.3)	3 (4.2)	0.341	109 (9.6)	7 (4.5)	0.253
Electrolyte abnormalities	603 (46.9)	577 (47.6)	26 (36.1)	< 0.001	542 (47.9)	61 (39.6)	< 0.001
MELD[b] score, mean ± SD	9.9 ± 5.7	10.4 ± 5.7	9.6 ± 5.1	0.759	10.4 ± 5.8	9.7 ± 5.4	0.735
Child-Pugh-Turcotte Score, *n* (%)				< 0.001			< 0.001
A	273 (21.2)	268 (22.1)	5 (6.9)		263 (23.3)	10 (6.5)	
B	763 (59.4)	726 (59.9)	37 (51.4)		671 (59.3)	92 (59.7)	
C	249 (19.4)	219 (18.1)	30 (41.7)		197 (17.4)	52 (33.8)	

[a]Non-alcoholic steatohepatitis, drug-induced liver injury, autoimmune liver disease, etc.
[b]Model for end-stage liver disease.
HBV, hepatitis B virus; HCV, hepatitis C virus.

and other causes (164, 12.8%). Among the patients readmitted within 30 and 90 days, a higher proportion had volume-related issues, and HE was the primary reason for their initial hospitalization. The mean cost for first admission was 25,035 ± 51,529 Renminbi (RMB). Among the patients readmitted within 30 and 90 days, there was a higher prevalence of longer initial hospital stays (30-day: 19.8 ± 13.1 vs. 15.1 ± 12.0 days, $p = 0.001$; 90-day: 17.8 ± 11.5 vs. 15.0 ± 12.2 days, $p = 0.007$) and higher initial hospitalization costs (30-day: 33833 ± 29,829 vs. 24,509 ± 52,504 RMB, $p = 0.136$; 90-day: 27461 ± 26,636 vs. 24,702 ± 54,056 RMB, $p = 0.533$). The primary causes of readmission within 30 days were volume-related issues ($n = 30$, 41.7%), liver function deterioration ($n = 12$, 16.7%), and HE ($n = 11$, 15.3%). For readmissions within 90 days, the major causes were volume-related issues ($n = 80$, 51.9%), deterioration of liver function ($n = 20$, 12.9%), and other miscellaneous causes ($n = 15$, 9.7%). Of the patients who were readmitted within 30 days, 33 (45.8%) were readmitted for the same cause. Similarly, among patients readmitted within 90 days, 72 (46.8%) were readmitted for the same cause (Table 2).

3.3 Predictors of 30-day and 90-day readmission

The results of the logistic regression analysis for the predictors of readmission within 30 and 90 days are presented in Table 3. Significant predictors of readmission within 30 days included HE and SBP. For readmission within 90 days, the significant predictors included diabetes, HE, ascites, and SBP (Table 3).

3.4 Predictors of length of hospitalization at the first admission

Table 4 demonstrates that hypertension ($p = 0.001$) and SBP ($p < 0.001$) were significant predictors of the length of hospitalization of patients during their initial admission.

4 Discussion

Data and evidence on the rates and reasons for readmission among patients with cirrhosis in China are currently lacking. Moreover, the causes of cirrhosis in China differ significantly from those in Europe and the United States, with a higher proportion of cirrhosis cases attributed to viral hepatitis. Our study, which included a large sample size, identified the predictors of readmission in Chinese patients with cirrhosis. These findings provide valuable insights for the targeted management of complications, with the aim of reducing readmission risks and optimizing medical resource utilization for patients with cirrhosis in China. This retrospective study revealed that patients with cirrhosis who presented with HE, ascites, or SBP had a higher risk of rehospitalization. Additionally, the study found that hypertension and SBP could predict the length of hospitalization during initial admission. Along with variceal hemorrhage, ascites and HE are manifestations of hepatic decompensation in patients (25).

TABLE 2 Hospitalization characteristics.

Index hospitalization	All *n* = 1,285	30-days readmission			90-days readmission		
		Not readmitted *n* = 1,213	Readmitted *n* = 72	*p*-value	Not readmitted *n* = 1,131	Readmitted *n* = 154	*p*-value
Major cause for the first admission, *n* (%)				0.011			< 0.001
Volume-related	568 (44.2)	530 (43.7)	38 (52.8)	(--)	485 (42.9)	83 (53.9)	(--)
Variceal bleeding	46 (3.6)	46 (3.8)	0 (0)	(--)	42 (3.7)	4 (2.6)	(--)
Hepatocellular carcinoma	58 (4.5)	53 (4.4)	5 (6.9)	(--)	48 (4.2)	10 (6.5)	(--)
Hepatic encephalopathy	101 (7.9)	90 (7.4)	11 (15.3)	(--)	82 (7.3)	19 (12.3)	(--)
Liver function deterioration	285 (22.2)	272 (22.4)	13 (18.1)	(--)	261 (23.1)	24 (15.6)	(--)
Infection	63 (4.9)	63 (5.2)	0 (0)	(--)	63 (5.6)	0 (0)	(--)
Other	164 (12.8)	159 (13.1)	5 (6.9)	(--)	150 (13.3)	14 (9.1)	(--)
Cost for the first admission (RMB[a]), mean ± SD	25,035 ± 51,529	24,509 ± 52,504	33,833 ± 29,829	0.136	24,702 ± 54,056	27,461 ± 26,636	0.533
Length of stay (days) mean ± SD	15.3 ± 12.1	15.1 ± 12.0	19.8 ± 13.1	0.001	15.0 ± 12.2	17.8 ± 11.5	0.007
Major cause for readmission, *n* (%)							
Volume-related[b]	(--)	(--)	30 (41.7)	(--)	(--)	80 (51.9)	(--)
Variceal bleeding	(--)	(--)	3 (4.2)	(--)	(--)	5 (3.2)	(--)
Hepatocellular carcinoma	(--)	(--)	3 (4.2)	(--)	(--)	8 (5.2)	(--)
Hepatic encephalopathy	(--)	(--)	11 (15.3)	(--)	(--)	13 (8.4)	(--)
Deterioration of liver function[c]	(--)	(--)	12 (16.7)	(--)	(--)	20 (12.9)	(--)
Infection	-	-	6 (8.3)	-	-	9 (5.8)	-
Other	-	-	7 (9.7)	-	-	15 (9.7)	-
Readmission for the same cause, *n* (%)	-	-	33 (45.8)	-	-	72 (46.8)	-

[a] Renminbi. [b] ascites, hepatic hydrothorax, edema, or spontaneous bacterial peritonitis. [c] (1) an increase in Child-Pugh score from pre-visit of 2 points or more; (2) total bilirubin (TBil) ≥51 μmol/L or an increase in TBil from pre-visit of ≥34.2 μmol/L; (3) any increase in prothrombin time from pre-visit of ≥3S.

TABLE 3 Predictors of 30-day and 90-day readmission in the logistic regression analysis.

Characteristics	β	95% CI of β	p-value	OR
30-day readmission				
Hepatic encephalopathy	0.827	0.139–1.515	0.018	2.36
Spontaneous bacterial peritonitis	1.255	0.611–1.899	0.000	3.82
90-day readmission				
Diabetes	0.608	0.191–1.025	0.004	2.86
Hepatic encephalopathy	0.641	0.149–1.132	0.011	2.55
Ascites	1.662	0.203–3.121	0.025	2.23
Spontaneous bacterial peritonitis	0.808	0.338–1.279	0.001	3.37

Based on these results, it is crucial to focus on controlling the progression of patient complications, particularly HE, ascites, and SBP, in order to reduce readmissions in patients with cirrhosis and alleviate their financial burden. Diuretics, antibiotics, and albumin should be administered early and reasonably to control the progression of ascites and SBP. To control the progression of HE, the American Association for the Study of Liver Diseases recommends the assessment of covert HE in patients with cirrhosis, as covert HE is a precursor of overt HE (26). A prospective trial suggested that a high dose/frequency treatment of overt HE would reduce readmission within 30 days in patients with cirrhosis (27). By implementing these strict measures to manage the development of complications in patients with cirrhosis, we can improve their physical condition and overall quality of life, as well as reduce their readmission.

HE is a significant complication of decompensated cirrhosis and is associated with poor outcomes (28). Overt HE results in hospital admissions and high 1-year and 5-year mortality (29). The interplay among increased ammonia concentrations, alterations in amino acid metabolism, and inflammation is central to this disease (30). The presence of HE in patients with cirrhosis is thought to be associated with hospital readmission, increased mortality, impaired quality of life, and greater fall risk (31). A study concluded that HE was most strongly associated with readmission within 30 (OR 3.23, 95%CI 2.97–3.52) and 90 days (OR 3.07, 95%CI 2.86–3.30) (15). Patients who were diagnosed with HE had median survivals of 0.95 and 2.5 years for those aged <65 or ≥ 65 years, respectively (32). A cohort study of 1,560 patients concluded that patients with grade 3–4 HE during hospitalization had higher MELD scores and mortality (72%) than those with grade 1–2 or no HE (33). HE was also the main reason for repeated readmission within 3 months (34). Our study aligns with these findings, emphasizing the importance of early identification and intervention in controlling the progression. According to the practice guidelines, controlling precipitating factors of overt HE is of paramount importance. Special drug treatments, such as lactulose, antibiotics, and rifaximin, are part of management (26). This proactive approach serves as a robust strategy to effectively reduce readmissions in patients with cirrhosis.

Ascites and SBP are significant complications commonly observed in patients with cirrhosis and are closely linked to their worsening condition. Specifically, ascites has been associated with a higher risk of 30-day readmission (15). Other features of cirrhosis, including gastrointestinal bleeding, infections, and renal failure, pose significant risks to the patients' overall outcomes. These factors contribute to higher readmission rates, and a consistent relationship exists between readmission and subsequent mortality (9). SBP is a complication that specifically occurs in patients with ascites and tends to recur (35). Reports have indicated that the 30-day readmission rate for SBP is 25.6% (36). Ascites is a common complication of decompensated cirrhosis and increases the risk of further complications such as SBP and umbilical hernias, which may lead to readmission for further therapy (37). Our study concluded that ascites and SBP were associated with rehospitalization in patients with cirrhosis, which is similar to the reports above. Consequently, when patients develop ascites, it is essential to implement preventive measures against infections to mitigate the risks associated with SBP and reduce the likelihood of readmission. In this study, esophageal variceal bleeding did not increase the risk of readmission. This may be due to variceal eradication through early endoscopic control after endoscopic band ligation, which has been identified as a significant predictor of 90-day readmission in patients with cirrhosis. Similarly, a comprehensive review concluded that cirrhotic patients with diabetes had a higher risk of HE, elevated portal pressure, gastrointestinal bleeding, and increased susceptibility to bacterial infections and HCC (38). These factors contributed to the patient readmission rates. In a retrospective cohort study involving 12,442 patients who underwent liver transplantation, recipients with diabetes had longer hospital stays, higher peri-transplant mortality, inferior graft outcomes, and lower patient survival (39). Additionally, another study highlighted that patients with liver cirrhosis and type 2 diabetes mellitus (T2DM) had a significantly increased median length of hospital stay, doubled rate of non-cirrhosis-related admissions, and 1.35-fold increased rate of cirrhosis-related admissions compared to those without T2DM (40). While our study did not find diabetes to be a predictor of length of hospitalization, it revealed that diabetes affects long-term readmission in patients with cirrhosis. These findings suggest that patients with cirrhosis who also had diabetes were at a higher risk of prolonged hospital stay, and their overall condition would deteriorate if diabetes remained uncontrolled. Therefore, it is crucial to rigorously manage the development of comorbidities in patients with cirrhosis and diabetes to delay disease progression and improve outcomes.

In our cohort, we observed that hypertension and SBP were predictors of the length of hospitalization in patients with cirrhosis. Hypertension is a prevalent chronic disease worldwide and is often associated with other conditions, such as cardiovascular disease and non-alcoholic fatty liver disease (41, 42). Recent research has revealed several factors related to the length of hospital stay in patients with cirrhosis, including malnutrition, diabetes, infection, paracentesis use,

TABLE 4 Predictors of length of hospitalization at the first admission.

Characteristics	B[a]	SE	β estimate	p-value	95.0%CI for β
Males	0.627	0.696	0.90	0.367	−0.737–1.9925
Age (years)	−0.040	0.026	−1.55	0.122	−0.092–0.011
Baseline liver disease					
Alcohol	−0.764	0.761	−1.00	0.315	−2.257–0.728
Viral	0.320	0.647	0.49	0.621	−0.949–1.589
Co-morbidities					
Hypertension	1.781	0.642	2.77	0.006	0.521–3.042
Diabetes	−0.722	0.662	−1.09	0.276	−2.021–0.577
Chronic kidney disease	0.909	0.724	0.94	0.350	−0.998–2.817
Complications					
Hepatocellular carcinoma	0.124	0.787	0.16	0.875	−1.420–1.669
Hepatic encephalopathy	0.401	0.782	0.51	0.608	−1.134–1.936
Ascites	0.623	1.127	0.55	0581	−1.589–2.8347
Variceal bleeding	1.167	1.114	1.05	0.295	−1.019–3.353
Spontaneous bacterial peritonitis	3.572	0.806	4.43	0.000	1.991–5.154
Hepatic hydrothorax	0.137	0.994	0.14	0.890	−1.813–2.087
Electrolyte abnormalities	0.359	0.600	0.60	0.550	−0.819–1.536
Acute kidney injury	−4.010	4.403	−0.91	0.363	−12.648–4.628
MELD[a] score	0.017	0.594	0.28	0.781	−0.100–0.133
Child-Pugh-Turcotte score					
B	−0.365	0.672	−0.54	0.587	−1.684–0.953
C	−0.152	1.056	0.14	0.886	−1.920–2.224
Constant	13.264	1.997	6.64	0.000	9.345–17.182

[a]Model for end-stage liver disease.
HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HE, hepatic encephalopathy; SBP, spontaneous bacterial peritonitis; CKD, chronic kidney disease; MELD: End-Stage Liver Disease; INR, international normalized ratio; EGVB, esophagogastric variceal bleeding; TBil, total bilirubin; PT, prothrombin time; RMB: Renminbi; T2DM, type 2 diabetes mellitus.

SBP, and bariatric surgery (38, 43–46). Interestingly, there is limited research specifically exploring the relationship between hypertension and length of hospitalization in patients with cirrhosis. According to the literature, patients with cirrhosis often experience decreased splanchnic resistance and increased peripheral resistance. These changes are influenced by altered circulating vasoactive substances and the reactivity of the vasomotor and regulatory systems. Consequently, patients may present with hypotension, normotension, or hypertension (47, 48). One possible reason for the scarcity of studies is that arterial hypertension is not commonly observed in patients with cirrhosis. Some studies have suggested that hypertension exerts a protective effect against the occurrence of ascites or other complications related to circulatory dysfunction (49). Nevertheless, certain types of liver diseases, such as alcoholic fatty liver and HBV with renal involvement, may be accompanied by arterial hypertension (47). Our study population consisted predominantly of patients with alcohol-related and viral liver diseases, accounting for 74.3% of enrolled patients. This could explain why hypertension emerged as a significant predictor of the length of hospitalization in our study. Combined with previous literature, we believe that the prolonged hospital stay of patients with cirrhosis and hypertension may be related to kidney injury caused by hypertension and may also be related to the damage of some target organs by inflammatory factors released by the body during hypertension (48). However, further investigations are necessary to validate and elucidate the relationship between hypertension and length of hospitalization in patients with cirrhosis, particularly to explore its association with different types of liver diseases, such as alcohol-related and viral liver diseases. A potential research direction may be that hypertension leads to abnormal vasomotor function, which leads to abnormal secretion of hormones regulating blood pressure, adversely affecting liver function, and thus prolonging hospital stay in patients with cirrhosis.

Our study has several limitations. First, the indications for readmission varied over time, even within the same hospital, which was a major limitation of this retrospective analysis. Second, a notable omission in our study was the lack of data on specific treatments received by the patients, which could potentially serve as predictors of readmission and duration of hospitalization. Future studies should incorporate treatment data to provide more comprehensive insight. Third, the underlying mechanisms by which HE and SBP affect readmission rates in patients with cirrhosis have not yet been explored. Further investigations into these mechanisms are necessary as they could help develop more effective strategies to reduce readmission rates. Mortality is a key factor that may have influenced the outcomes of this study. However, because this was a retrospective

study, we were unable to obtain mortality data, which is another limitation. Post-discharge management, including treatment of the underlying liver disease, medications for complications (such as beta-blockers, rifaximin, and diuretics), treatment of comorbidities, and patient adherence, could significantly affect the risk of readmission. Unfortunately, the lack of comprehensive post-discharge data prevented us from investigating this aspect. Moreover, non-liver-related deaths and readmissions are common among patients with cirrhosis. This area requires further exploration in future studies. Finally, although our study identified hypertension as a predictor of the length of hospitalization in patients with cirrhosis, we did not extensively explore this relationship. Future research should thoroughly examine the association between hypertension and hospitalization duration, particularly in the context of different liver diseases, such as alcohol-related and viral liver diseases. Our study highlighted hypertension as a predictor of the length of hospitalization in patients with cirrhosis; however, we did not extensively investigate this relationship. Therefore, additional research should be conducted to thoroughly explore the association between hypertension and the length of hospitalization, particularly considering different types of liver diseases, such as alcohol-related and viral liver diseases.

5 Conclusion

Patients with cirrhosis and conditions such as HE, ascites, SBP, and diabetes may have a higher risk of rehospitalization. Additionally, hypertension and SBP appear to be associated with the length of hospitalization in these patients. Clinicians might benefit from focusing on the early management of complications such as HE, SBP, and diabetes in patients with cirrhosis. However, these conclusions should be interpreted with caution, and additional studies are required to confirm these associations.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by ethics committee of Peking University People's Hospital (No. 2023PHB214-001). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this is a retrospective study and we collected enrolled patients' sociodemographic, clinical, and hospitalization characteristics.

Author contributions

SW: Writing – original draft, Writing – review & editing. LZ: Writing – original draft, Writing – review & editing. JL: Writing – original draft. JF: Formal analysis, Methodology, Writing – original draft. JG: Methodology, Supervision, Writing – review & editing, Formal analysis, Funding acquisition, Investigation, Resources, Writing – original draft. RH: Methodology, Supervision, Writing – review & editing, Formal analysis, Funding acquisition, Investigation, Resources, Writing – original draft.

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Conflict of 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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