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REVIEW

COVID-19 and liver injury: Pathophysiology, risk factors, outcome and management in special populations

Romina Roshanshad, Amirhossein Roshanshad, Reza Fereidooni, Mahnaz Hosseini-Bensenjan

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Abstract

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 is an ongoing health concern. In addition to affecting the respiratory system, COVID-19 can potentially damage other systems in the body, leading to extra-pulmonary manifestations. Hepatic manifestations are among the common consequences of COVID-19. Although the precise mechanism of liver injury is still questionable, several mechanisms have been hypothesized, including direct viral effect, cytokine storm, hypoxic-ischemic injury, hypoxia-reperfusion injury, ferroptosis, and hepatotoxic medications. Risk factors of COVID-19-induced liver injury include severe COVID-19 infection, male gender, advanced age, obesity, and underlying diseases. The presentations of liver involvement comprise abnormalities in liver enzymes and radiologic findings, which can be utilized to predict the prognosis. Increased gamma-glutamyltransferase, aspartate aminotransferase, and alanine aminotransferase levels with hypoalbuminemia can indicate severe liver injury and anticipate the need for intensive care units' hospitalization. In imaging, a lower liver-to-spleen ratio and liver computed tomography attenuation may indicate a more severe illness. Furthermore, chronic liver disease patients are at a higher risk for severe disease and death from COVID-19. Nonalcoholic fatty liver disease had the highest risk of advanced COVID-19 disease and death, followed by metabolic-associated fatty liver disease and cirrhosis. In addition to COVID-19-induced liver injury, the pandemic has also altered the epidemiology and pattern of some hepatic diseases, such as alcoholic liver disease and hepatitis B. Therefore, it warrants special

vigilance and awareness by healthcare professionals to screen and treat COVID-19-associated liver injury accordingly.

Key Words: SARS-CoV-2; COVID-19; Liver injury; Chronic liver disease; Management; Liver transplant

Core Tip: Severe acute respiratory syndrome coronavirus-2 can involve the liver and cause damage through different mechanisms. Liver injury can be diagnosed based on alterations in the liver function tests, which can also predict the disease severity and fatality. In patients without underlying liver disease, liver injury is typically mild and can be treated with supportive care. However, it requires additional awareness and appropriate therapy in patients with chronic liver diseases, including autoimmune hepatitis, viral hepatitis, liver cirrhosis, liver transplantation, and nonalcoholic fatty liver disease, which we have discussed in detail.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has tremendously influenced global public health since its emergence in December 2019. Despite the effectiveness of worldwide vaccinations, the disease is still a substantial threat[1]. As of 6 January 2023, the World Health Organization (WHO) recorded over 657 million confirmed cases of COVID-19 and over 6.6 million deaths[2].

COVID-19 was first recognized as a respiratory disease with variable manifestations, from asymptomatic and mild symptoms to acute respiratory distress syndrome and death. However, further investigations determined that COVID-19 can cause various extra-pulmonary manifestations and result in multi-organ dysfunction[3]. Various theories have been suggested to explain how COVID-19 causes gastrointestinal (GI) system involvement. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) penetrates the host cells *via* angiotensin converting enzyme 2 (ACE2) receptors, which exist in different tissues, including the GI system. This may result in GI manifestations such as nausea, vomiting, diarrhea, anorexia, and hepatic manifestations[4]. After the lungs, the liver is the second most frequent organ impacted by COVID-19[5]. Liver involvement usually presents as mild to moderate elevations of liver enzymes. Although, in certain circumstances, including patients with severe COVID-19 infection and underlying comorbidities (*i.e.*, diabetes and hypertension) significant elevations of liver enzymes and liver dysfunction are more probable to happen[6,7]. COVID-19-induced liver injury may develop in patients regardless of the presence of underlying liver diseases; however, the likelihood of poorer outcomes is higher in patients with underlying chronic liver disease (CLD)[5,8]. Chronic liver diseases, including viral hepatitis, autoimmune hepatitis, liver cirrhosis, and fatty liver disease constitute a significant worldwide health burden. About 3% of COVID-19 patients have CLD, and this group has a higher risk of developing severe disease and death[9]. Moreover, these individuals have impaired immune systems due to their use of immunosuppressive drugs. Therefore, it is essential to consider stringent monitoring and develop appropriate treatments for these patients[10].

In this review, we aimed to comprehensively investigate different related aspects of liver injury in COVID-19. We discuss the pathophysiology, epidemiology, clinical manifestations, management, and outcomes of COVID-19 patients with liver injury. We also covered important topics like the interaction between COVID-19 and various types of liver disease, as well as unique considerations for particular populations with CLD and liver transplant (LT) recipients.

MECHANISMS AND PATHOPHYSIOLOGY OF LIVER INJURY IN COVID-19 PATIENTS

Although the exact mechanism of liver injury in COVID-19 is yet to be understood, several pathways have been proposed. The direct viral effect, drug hepatotoxicity, systematic inflammatory response (cytokine storm), decompensation of pre-existing liver disease, and hypoxic liver injury are among the suggested hypotheses[11]. Figure 1 demonstrates the proposed mechanisms of liver injury in COVID-19.

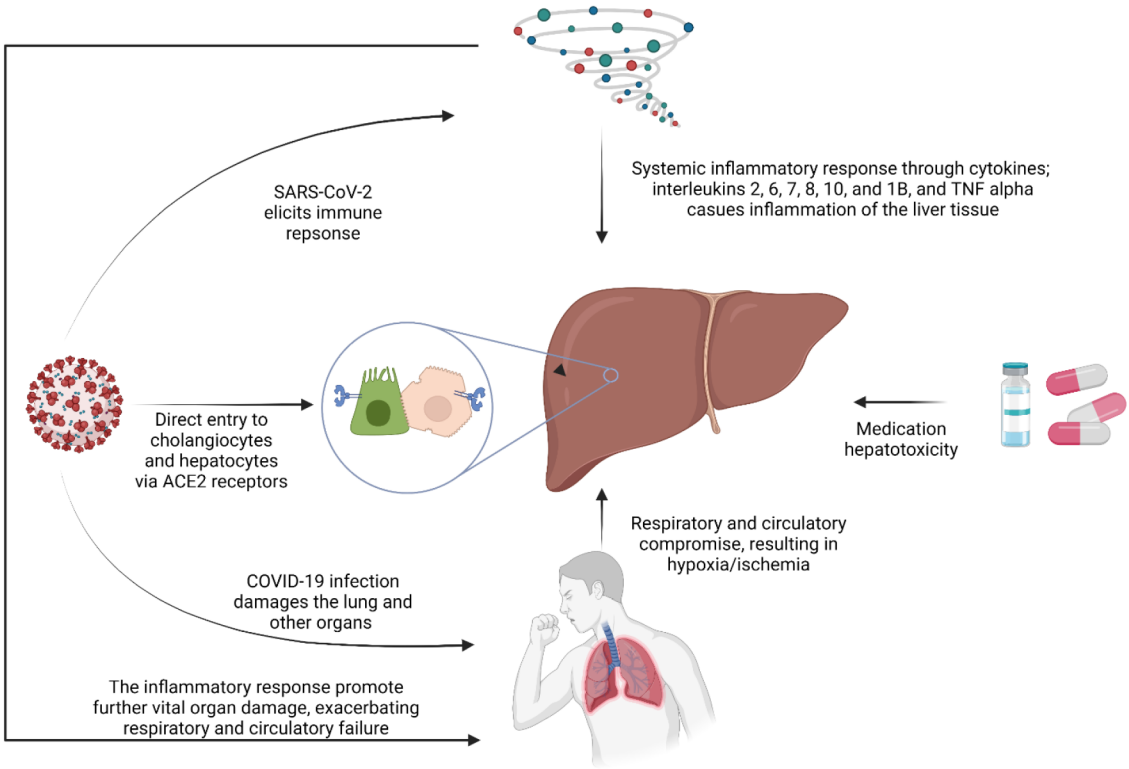

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Figure 1 Proposed mechanisms of liver injury in coronavirus disease 2019 patients. SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; ACE2: Angiotensin converting enzyme 2; COVID-19: Coronavirus disease 2019; TNF alpha: Tumor necrosis factor alpha.

Direct viral effect

Although almost none of the current histopathological reports has shown a typical hepatitis picture[12], some evidence argues in favor of liver tropism and the direct effect of the virus on the liver. Firstly, the SARS-CoV-2 receptor, ACE2, is found on the surface of the hepatic Kupffer cells, hepatocytes, and cholangiocytes which helps the virus enter these cells and, as a result, makes the liver a potential target organ for the virus[13-15]. Secondly, Wang *et al*[16] discovered the SARS-CoV-2 spike structures in the cytoplasm of hepatocytes in two COVID-19 cases. The spatial presence of SARS-CoV-2 RNA and spike protein was also proved by previous studies in hepatic cells, which implies replication of the virus and direct infection of hepatic parenchyma[13,17]. Wanner *et al*[13] discovered a lower viral load in the liver than in the lungs of one patient, suggesting this may be the reason we do not typically observe cytopathic changes (*i.e.*, hepatitis pattern) in the liver of COVID-19 patients.

Systemic inflammatory response (cytokine storm)

In response to COVID-19 and in order to hinder viral replication and evoke the adaptive immune response, the innate immune system is activated[18]. Severe cases of COVID-19 are associated with an exaggerated immune response indicated by high levels of C-reactive protein (CRP), pro-inflammatory T helper 17 cells, and cytokines[18,19]. Cytokines in severe cases of COVID-19 include interleukins (IL)-2, 6, 7, 8, 10, and 1B and Tumor necrosis factor alpha (TNF-α)[18-20]. Pathological studies have demonstrated non-specific inflammatory changes in the hepatocytes, including steatosis, lymphocyte infiltration, and Kupffer cell hyperplasia[19]. This immune system dysregulation can result in multiple organ involvement, including the liver. The cytokine storm not only affects the liver by triggering the inflammatory response and recruiting macrophages; but also plays a role in further indirect damage by promoting thrombotic events, circulatory changes, and failure of other organs[20].

Hypoxic-ischemic injury, hypoxia-reperfusion injury, and liver congestion

While shock as the result of the COVID-19 infection itself is not a common finding[21], it is a common entity in intensive care units (ICU)[22]. COVID-19 patients are susceptible to all types of shock (*i.e.*, cardiogenic, septic, hypovolemic, and obstructive)[21,23,24]. While shock reduces liver perfusion, respiratory failure can also produce hypoxic harm to the liver, even in the absence of ischemia[22,25]. On the other hand, COVID-19 is known to induce microangiopathy and thromboembolism that further compromises the liver blood supply[26]. In the context of COVID-19, liver damage and coagulopathy are connected. Rise in transaminases have been shown to correlate with abnormal coagulopathy markers, such as prothrombin time, international normalized ratio, fibrinogen, D-dimer, fibrin/

fibrinogen degradation products and platelet count[27]. Different organ involvements in COVID-19, including cardiac, pulmonary, and vascular involvement, paired with the high metabolic activity of the liver, makes it a highly susceptible organ to hypoxic-ischemic damage[28]. In the autopsy of COVID-19 patients, ischemic-type hepatic necrosis and lipid droplet accumulation (steatosis) have been found in histopathologic evaluations, both findings in favor of hypoxic-ischemic liver damage[12,29]. However, the hallmark of hypoxic hepatitis is a significant increase in liver enzymes, and the increase reported in the COVID-19 scenario is notably less[30]. Hence some have hypothesized that hypoxia-reperfusion is another explanatory mechanism[23]. Impairment of the venous drainage of the liver can contribute to blood stasis and hepatic congestion. Hepatic congestion is caused by the stasis of blood within the liver parenchyma due to the compromise of hepatic venous drainage[31]. Congestion of the hepatic sinusoids was estimated at 34.7% in a histopathologic study[32]. Cardiac events resulting in right-sided heart failure, decompensation of heart failure, and pulmonary thromboembolism can contribute to liver congestion in COVID-19 patients[23]. In a review by Kukla *et al*[33], hepatic dysfunction was associated with mechanical ventilation, especially with high rates of positive end-expiratory pressure (PEEP). They hypothesized that high PEEP (18-20 cm H_2O) causes high right atrial pressure resulting in liver congestion in a mechanism similar to right-sided heart failure. In a hemodynamic study of COVID-19 patients, mechanical ventilation and PEEP were associated with left ventricular underfilling[25].

Ferroptosis

Ferroptosis is a novel form of cell death, which is characterized by iron accumulation and lipid peroxidation[34]. The oxidative stress caused by iron overload is an important trigger for liver injury as well as other vital organ damage[35]. COVID-19 is believed to impact iron metabolism[36]. In the condition of cytokine storm, IL-6 stimulates the production of hepcidin in the liver, which is an inhibitor of iron export and leads to iron sequestration inside cells[37]. It is hypothesized that SARS-CoV-2 triggers the recognition of blood iron-binding molecules by receptors in many organs, including the liver, thereby causing an influx of iron ions. The accumulated iron, along with agents like lipid and hydrogen peroxide, triggers the Fenton reaction, producing massive lipid reactive oxygen species that cause cell membrane damage[38]. In conclusion, ferroptosis is a potentially important mechanism of organ damage in COVID-19; however, the extent of its role and whether treatments that inhibit ferroptosis can be helpful in preventing organ damage in COVID-19 remains to be determined[37,39].

Medications

Medication hepatotoxicity has strong evidence as the cause of liver injury in the context of COVID-19 [40]. Owing to the novel nature of the COVID-19 infection and the lack of evidence-based guidelines, various medications have been used for treatment, many of which have potential hepatotoxic properties. These include antivirals (including remdesivir, lopinavir/ritonavir, Favipiravir), hydroxychloroquine, antibiotics (*e.g.*, azithromycin), corticosteroids, tocilizumab, and antipyretics, specifically acetaminophen[23,40,41]. Remdesivir has been associated with transient increases in liver enzymes in Gilead company trials in less than 5% of participants and was indicated to possibly be cytotoxic to human hepatocytes at clinically relevant exposures[42,43]. Consistently, liver injury in remdesivir-treated COVID-19 cases was mostly mild, according to published literature[44-46]. Wang *et al*[34] reported that 7% of a remdesivir-treated group developed grade 1-2 aspartate aminotransferase (AST) elevation compared to 12% in a placebo-controlled group, and 1% developed grade 1-2 alanine aminotransferase (ALT) elevation. Case reports have revealed that associate Favipiravir, another antiviral agent used to treat COVID-19, with liver injury[47,48]. However, a systematic review on the safety of Favipiravir in COVID-19 failed to prove the association between the drug and liver injury[49]. The use of lopinavir/ritonavir has been linked to liver toxicity in multiple studies of COVID-19 patients [40]. Serum aminotransferases increase in a large number of individuals using antiretroviral regimens containing ritonavir. Moderate to severe elevations in the serum aminotransferase levels are detected in up to 15% of patients treated with full dosages of ritonavir[50]. In the setting of COVID-19, Cai *et al*[51] also found lopinavir/ritonavir to be associated with increased odds of liver injury. Yip *et al*[52] showed that the use of lopinavir/ritonavir ± ribavirin + interferon beta was independently associated with elevated liver enzymes. The use of systemic corticosteroids is highly encouraged in COVID-19, especially in patients requiring oxygen supplement therapy[53]. A cohort study in Hong Kong reported the independent association of corticosteroids with elevated AST/ALT[52]. However, extensive data on the hepatotoxicity of corticosteroids is non-existent, and it's usually confined to case reports[53]. Some have even proposed them to treat drug-induced liver injury[54]. One potential way of corticosteroid-induced liver toxicity may be its role in inducing non-alcoholic steatohepatitis[53]. Tocilizumab, a humanized recombinant monoclonal antibody, is used to combat systematic inflammatory response in COVID-19 because of its anti-IL-6 properties[55]. Hepatotoxicity with transient, mild to moderate transaminase increase is its well-known side effect, but severe drug-induced liver injury is a rare event [55,56]. Hydroxychloroquine and chloroquine are the standard medications to treat malaria and had been explored as treatment options for COVID-19 due to their *in vitro* anti-SARS-CoV-2 properties[57]. Liver injury associated with hydroxychloroquine is uncommon and limited to case reports[58-60]. Azithromycin, a macrolide antibiotic, was also advocated for the treatment of COVID-19 owing to its cytokine-suppressing features, potentially preserving the epithelial cells and inhibiting lung fibrosis

[61]. Azithromycin is known to cause liver injury, with both hepatocellular and cholestatic patterns[62,63]. Ivermectin, an anti-parasite drug, was reported to be associated with one case of severe hepatitis; however, there is insufficient data to comment on the effects of ivermectin on the liver function of COVID-19 patients, and more research is needed to clarify this[40,64]. So far, there is no report in the literature about acetaminophen-associated hepatotoxicity in COVID-19 patients; this is likely because acetaminophen-induced hepatotoxicity is highly dose-dependent, and its safe dose is well-established [65]. Additionally, it should be highlighted that, despite dosages used in patients normally belonging within safe ranges, combination therapy with various hepatotoxic drugs may have a synergistic effect.

COVID-19 AND LIVER MANIFESTATIONS

COVID-19 is usually regarded as a respiratory disease; however, subsequent research revealed extra-pulmonary manifestations of COVID-19, including cardiovascular, gastrointestinal, renal, ocular, neurological, psychiatric, dermatological, and endocrinology symptoms[66,67]. GI manifestations of COVID-19 are among the most common extra-pulmonary manifestations, and they can emerge even before the appearance of respiratory symptoms. Also, they can be the sole manifestation in some COVID-19 patients[68]. It seems that patients with COVID-19 who experience GI symptoms have a higher risk of elevated liver enzymes and liver injury[18,69]. The prevalence of liver injury in COVID-19 patients ranges widely from 21.5% to 45.71%[70]. This wide range is because of the specific characteristics of different populations and cut-off level discrepancies[71]. Liver injury commonly manifests as abnormalities in liver enzymes in the absence of particular clinical symptoms. Hence, close monitoring of liver enzymes in COVID-19 patients is essential for timely diagnosis of liver injury. In a meta-analysis by Yadav *et al*[70], the prevalence of liver enzymes abnormalities among COVID-19 patients ranged from 37.2% to 76.3%. In another meta-analysis, an elevation in the liver enzymes was reported in about 25% of COVID-19 patients, and the prevalence of increased AST and ALT was 23.2% and 21.2%, respectively. Gamma-glutamyltransferase (GGT) was elevated in 15%, total bilirubin in 9.7%, and alkaline phosphatase (ALP) in 4% of the patients[69].

RISK FACTORS FOR LIVER INJURY AND PREDICTORS OF DISEASE SEVERITY

Certain risk factors can predispose patients to develop liver injury. Some laboratory findings, such as lymphopenia, elevated AST/ALT ratio, and higher erythrocyte sedimentation rate and CRP levels are linked to the development of liver injury in COVID-19 patients. It is hypothesized that a systemic inflammatory response and cytokine storm are the cause of liver damage[70,72]. In addition, male gender, obesity, and advanced age are the risk factors for liver injury in COVID-19 patients[51]. The higher odds of COVID-19 induced liver injury among males may be due to the higher prevalence of existing risk factors, such as nonalcoholic fatty liver disease (NAFLD) and alcohol intake[73,74]. Previous studies have linked abnormalities in liver enzymes and liver injury to disease severity and mortality[75]. The abnormalities in liver function tests (LFT) can be used to predict the outcome of the disease. In a study conducted by Cai *et al*[51], the patients who had hepatocellular and mixed patterns of liver involvement were at higher risk of developing severe disease. A hepatocellular pattern was determined as an increase in aminotransferases (ALT/AST) levels higher than three times the upper limit of normal (ULN), while a mixed pattern was determined as an increase in aminotransferases greater than three times the ULN and ALP/GGT greater than twice the ULN.

Weber *et al*[76] demonstrated the correspondence between abnormal baseline liver enzymes and disease progression in patients without underlying liver disease. Increased GGT, AST, and ALT levels with hypoalbuminemia upon admission predicted the severity of the illness and the requirement for ICU hospitalization. Other studies have confirmed the link between low albumin levels and the severity of COVID-19. Hypoalbuminemia in severely ill COVID-19 patients is likely due to a combination of impaired hepatic albumin production and dietary deficiencies[18,77]. Phipps *et al*[75] revealed that higher levels of peak ALT and markers of inflammation, such as ferritin and IL-6, were strongly linked to progression to severe liver injury and a poorer outcome.

RADIOLOGIC FINDINGS OF THE LIVER IN COVID-19 PATIENTS

Some radiologic manifestations of liver damage have been reported in COVID-19 patients. On abdominal computed tomography (CT) scans of COVID-19 patients, hepatic hypodensity and fat stranding around the gallbladder were observed[78]. Some findings, such as a decrease in liver-to-spleen attenuation ratio and liver CT attenuation, may be relevant to the severity of the disease[79,80]. Chen *et al*[72] demonstrated that hepatic steatosis on CT scan was observed in 11.3% of COVID-19 cases, which enhanced the risk of hepatic dysfunction. In addition, they mentioned that while a decrease in

hepatic attenuation on a baseline CT scan is rampant, it is usually a temporary condition that improves on subsequent CT scans. The most prevalent findings of abdominal ultrasound of COVID-19 patients in ICU were hepatomegaly and biliary abnormalities, including common bile duct dilatation, gallbladder distention, and wall thickening[81]. Also, it was shown that in patients with mildly increased liver enzymes, hepatic ultrasonography was often not significant. However, in patients with a substantial rise in liver enzymes, hepatic ultrasound may detect vascular abnormalities or cholestatic changes, which is tied to higher fatality rates[82].

COVID-19 VACCINATION AND LIVER INJURY

With widespread vaccination against COVID-19, many reports of immune-mediated liver injury (ILI) associated with vaccination have emerged[83-87]. Most cases develop a hepatocellular pattern of injury [86]. The proposed hypothesis is that due to the similarity between S protein and liver specific proteins, the immune response elicited against the S protein, which is encoded by the vaccines, may cause autoimmune-like hepatitis[88]. Histopathological evaluation of the patients with ILI demonstrated portal lymphoplasmacytic infiltration and interface hepatitis[89]. The prognosis of immune-mediated vaccine-induced liver injury seems to be excellent with corticosteroid treatment, with only 4.3% death among patients who received steroids[89].

Roy *et al*[89] reviewed ILI following COVID-19 vaccinations. Most of the patients with ILI were female, with a mean age of 55.3 years. Moderna mRNA–1273 was the most common culprit for ILI following COVID-19 vaccinations, followed by Pfizer-BioNTech BNT162b2 mRNA and AstraZeneca ChAdOx1 nCoV-19 vaccine. Inactivated vaccines can also contribute to ILI; however, the reports are much more scarce than mRNA vaccines[90]. The most common presentation of ILI was jaundice, which was present in 78.3% of the patients, and bilirubin, ALT, and ALP levels were elevated. There is a dispute over the diagnosis of ILI following vaccination. Physicians should consider the clinical symptoms, liver function tests, histopathological findings, and chronological association between vaccine injection and presentations of the symptoms.

OUTCOME, MANAGEMENT, AND CONSIDERATIONS IN SPECIAL POPULATIONS

Liver involvement is a common finding in patients with COVID-19; however, it is frequently mild, transitory, and resolves without management[75,91]. Nevertheless, patients with underlying liver diseases, including hepatitis, cirrhosis, or LT recipients, are at higher risk of severe diseases. It is estimated that the probability of developing severe disease and death due to COVID-19 was 2.44 times greater in patients with CLD compared to those without underlying liver diseases [Odds ratio (OR) for severity = 2.44, 95%CI: 1.89-3.16; OR for mortality = 2.35, 95%CI: 1.84-3.00][92]. Among different underlying liver diseases, NAFLD was associated with the highest odds of severe disease and death due to COVID-19, followed by metabolic-associated fatty liver disease (MAFLD) and cirrhosis[92]. Severity and mortality rates after COVID-19 were not impacted by viral hepatitis significantly. Table 1 demonstrates the strength of the association between several major underlying liver diseases and the severity and mortality of COVID-19.

Autoimmune hepatitis

The most common presentations of COVID-19 in patients with autoimmune hepatitis (AIH) were respiratory (74%) and GI (26%) manifestations[93]. However, AIH patients are more likely to present with GI manifestations than the general population (26% *vs* 14%). The mortality rate and cause of death of the AIH group were not significantly different from the non-AIH CLD group. Age (OR *per* 10 years: 2.01, 95%CI: 1.07-3.81), Child-Pugh B (OR: 42.48, 95%CI: 4.41-409.53), and Child-Pugh C (OR: 69.30, 95%CI: 2.83-1694.50) cirrhosis were the determinants of mortality within AIH patients[93].

AIH is an immune-mediated liver disease, which is mainly responsive to immunosuppressive therapy[94]. Single corticosteroid therapy or in combination with azathioprine are the standard immunosuppressive treatments for AIH[95]. Other drugs used to treat AIH include mycophenolate mofetil (MMF), calcineurin inhibitors, and TNF-α blockers[95]. The immunosuppression status following the use of these drugs enhances the risk of bacterial and viral infections in these patients[95] and might theoretically lead to a more severe COVID-19. Therefore, it is crucial to closely monitor the immunosuppressed AIH patients affected by COVID-19. In patients with simultaneous AIH and COVID-19, immunosuppressive therapy should be given after evaluating the risks and benefits. It is suggested that immunosuppressive therapy can be lifesaving in severe AIH patients[96]. Thus, it is not wise to discontinue the treatment as it might predispose the patients to a higher risk of relapse. In conclusion, empirical reduction in the doses of immunosuppressive drugs in these patients during the course of COVID-19 can be potentially harmful[97]; however, the immunosuppression therapy can be delayed until the COVID-19 polymerase chain reaction (PCR) test becomes negative in milder forms of

Table 1 The association of different underlying liver diseases with clinical outcomes of coronavirus disease 2019

Underlying liver disease/condition	Findings
Autoimmune hepatitis	AIH *vs* other CLDs: No significant differences in hospital admission (76% *vs* 85%; *P* = 0.06), ICU admission (29% *vs* 23%; *P* = 0.240), and mortality (23% *vs* 20%; *P* = 0.643) rates; AIH *vs* non-CLDs: Higher hospitalization rate, but similar rate for other outcomes; Severity of AIH associates with COVID-19 mortality, as follows: Age OR *per* 10 years: 2.01 (95%CI: 1.07-3.81); Child-Pugh B cirrhosis OR: 42.48 (95%CI: 4.41-409.53); Child-Pugh C cirrhosis OR: 69.30 (95%CI: 2.83-1694.50)[93]
Viral hepatitis	The risk of severe COVID-19 is higher (RR: 1.68, 95%CI: 1.26-2.22)[191]; however, another meta-analysis showed no association between viral hepatitis and poorer outcomes (pooled OR = 1.29, 95%CI: 0.36-4.63)[92]
Cirrhosis	Cirrhotic patients experienced more severe disease (pooled OR = 3.09, 95%CI, 1.95–4.89)[92]; Severity of cirrhosis associates with COVID-19 severity, as follows: Child-Pugh A cirrhosis OR: 1.90 (95%CI: 1.03-3.52); Child-Pugh B cirrhosis OR: 4.14 (95%CI: 2.4-7.65); Child-Pugh C cirrhosis OR: 9.32 (95%CI: 4.80-18.08)[111]
Liver transplant	No significant difference in mortality rates between LT and non-LT participants (OR: 0.8, 95%CI: 0.6-1.08); The time between the transplantation and COVID-19 did not affect the mortality rate (OR: 1.5, 95%CI: 0.63-3.56); Severe COVID-19 infection was observed in 23% of the participants with LT[129]
NAFLD	NAFLD was associated with more severe COVID-19 (AOR: 2.60, 95%CI: 2.24-3.02), more ICU admission (AOR: 1.66, 95%CI: 1.26-2.20), but not higher mortality rates (AOR: 1.01, 95%CI: 0.65-1.58)[148]
MAFLD	MAFLD increased the risk of severe COVID-19 (OR: 1.80, 95%CI: 1.53-2.13). No association was found between the presence of MAFLD and the occurrence of COVID-19 death[192]
Pregnancy	29.7% of pregnant patients with COVID-19 had liver injury; Liver injury can predispose pregnant females to experience more severe COVID-19, however, their neonates do not have worsen prognosis[157]

COVID-19: Coronavirus disease 2019; AIH: Autoimmune hepatitis; AOR: Adjusted odds ratio; CLD: Chronic liver disease; ICU: Intensive care unit; LT: Liver transplant; MAFLD: Metabolic associated fatty liver disease; MMF: Mycophenolate mofetil; NAFLD: Non-alcoholic fatty liver disease; OR: Odds ratio; RR: Relative risk.

AIH[96].

In addition to the impacts of COVID-19 on the management of AIH during the pandemic, SARS-CoV-2 has been proposed as a possible trigger for AIH. In a study by Kabaçam *et al*[96], COVID-19 patients were diagnosed with AIH after presenting with high serum aminotransferase and IgG levels. It should be noted that there is an AIH-like liver injury that might occur following COVID-19 vaccination. The laboratory findings are similar to AIH in these cases, and there is a good response to corticosteroids in these patients[98,99].

Viral hepatitis B

The prevalence of hepatitis B virus in patients with COVID-19 ranges from 0.1% in a study in the United States to 12.2% in China[100,101]. Interestingly, these prevalence rates were not significantly higher than the general population. Furthermore, there is no well-established association between HBV infection and severe COVID-19 disease[101-104]. Surprisingly, some studies reported a milder course of COVID-19 in patients with HBV[101,103,105,106]. One hypothesis is that patients with HBV might experience a state of "immune exhaustion", which can be responsible for a lower chance of developing cytokine storm[107].

The treatment of COVID-19 with corticosteroids and other immunosuppressive drugs, including tocilizumab, may lead to the reactivation of HBV infection in these patients. Therefore, screening for HBV in COVID-19 patients with elevated liver enzymes in endemic HBV populations is highly recommended[104]. Several treatments were recommended for COVID-19 infection in HBV patients. A suggested method is drug repositioning, which means that the antiviral HBV drugs could also be used to treat COVID-19 infection[108,109]. In COVID-19 HBsAg-positive patients who are not receiving anti-HBV medication, continuous corticosteroid or immunosuppressive drugs consumption necessitates prophylaxis with tenofovir disoproxil fumarate, tenofovir alafenamide, and entecavir to reduce the likelihood of HBV reactivation and liver failure[104].

Liver cirrhosis

COVID-19 is one of the main contributors to the exacerbation of preexisting liver cirrhosis[110]. It is found that liver cirrhosis decompensation occurs in nearly half of the cirrhotic patients with COVID-19, one-fifth of whom might not develop any pulmonary manifestations[111]. Therefore, physicians should be advised to consider COVID-19 in patients with cirrhosis exacerbation, even in the absence of respiratory symptoms. Because of cirrhosis-associated immune dysfunction, patients with decompensated liver cirrhosis are more susceptible to COVID-19[112,113]. The mortality rate in COVID-19 patients with decompensated liver cirrhosis was shown to be about 50%[114]. The main predictor of mortality in cirrhotic patients with COVID-19 is the severity of underlying cirrhosis[111]. Child-Pugh C cirrhosis has the highest odds for mortality among patients with CLD (OR = 9.32, 95%CI: 4.80-18.08),

while the odds ratio for Child-Pugh A was 1.90 (95%CI: 1.03-3.52). Other predictors of mortality were higher age and concurrent alcoholic liver disease. One study reported that mortality, ventilation support, hospitalization, and ICU admission rates were significantly higher in patients with higher model for end-stage liver disease (MELD) scores, especially a score above ten[115]. However, whether COVID-19 can worsen the outcomes in hospitalized patients with cirrhosis remains controversial. While some reports demonstrate that COVID-19 can elevate mortality rates in cirrhotic patients[110,116,117], other studies found that COVID-19 did not significantly increase mortality in these patients[118,119]. Monitoring liver function tests, early detection of liver complications caused by a coronavirus, and broad-spectrum antibiotic therapy in case of secondary bacterial infection are highly recommended for successful management[112].

The humoral response to COVID-19 vaccines is 94% in patients with CLD or cirrhosis. The mRNA vaccines are more efficacious than inactivated vaccines in these patients[120].

LT

The success rate of transplantation is associated closely with the postoperative immunosuppression treatment to prevent organ rejection[121]. Since the emergence of the pandemic, there has been a debate on the use and dosing of immunosuppressive drugs for these patients, as they act like a double-edged sword[122]. While they can profoundly decrease the chance of organ rejection, severe immunosuppression can theoretically lead to uncontrolled viral replication and severe COVID-19[123,124]. MMF and calcineurin inhibitors, including tacrolimus are among the main immunosuppressive drugs used in LT patients[125,126]. MMF inhibits the proliferation of lymphocytes and suppresses cell-mediated immunity and antibody formation[127]. LT patients who were previously treated with MMF have a higher risk of experiencing severe COVID-19 infection, especially those who have received doses more than 1000 mg/day[127]. They also suggested a reduction in the dose of MMF or temporary conversion to other immunosuppressive drugs, including tacrolimus in LT patients[127]. On the other hand, a meta-analysis found that the continued administration of certain immunosuppressive drugs during COVID-19 resulted in a lower probability of severe disease[128]. Among the immunosuppressive drugs, the mammalian target of rapamycin inhibitor (mTORi) was the most effective in preventing severe disease, followed by calcineurin inhibitors, steroids, and antimetabolites.

Further studies, including a meta-analysis, indicated that the rate of severe COVID-19 and death was not higher in LT patients[129]. Most deaths due to COVID-19 were associated with the cytokine storm and inflammatory process, not the result of direct viral replication[130]. Therefore, not only is immunosuppression not harmful, but also it could prevent cytokine storm and reduce mortality. Guarino *et al*[131] demonstrated that LT patients were more likely to become symptomatic; however, they did not exhibit more severe disease and death due to COVID-19. They did not reduce the dose of immunosuppressive drugs unless in severe and critical patients. This heterogeneity among the results can be attributed to the baseline characteristics of the patients, including the presence of other comorbidities, mean age, time from the transplant to COVID-19, and immunosuppressive drug. The strengths of the associations of these factors were as follows: (1) Age > 70 [Hazard ratio (HR): 4.16, 95%CI: 1.78-9.73]; (2) Tacrolimus use (HR: 0.55, 95%CI: 0.31-0.99); (3) Diabetes (HR: 1.95, 95%CI: 1.06-3.58); (4) Chronic kidney disease (HR: 1.97, 95%CI: 1.05-3.67); and (5) Time between transplantation and COVID-19 (HR: 0.55, 95%CI: 0.31-0.99)[132,133]. Therefore, we suggest that physicians assess the risk of severe disease in LT patients by considering age, comorbidities, and the time between the transplant and COVID-19. It is not necessary to modify the immunosuppressive drugs for all the patients; they can be closely monitored for the occurrence of risk factors and manifestations of severe disease and, if present, reducing the dose or changing the drugs can be applied. Besides, tacrolimus-based or mTORi-based immunosuppressive regimens have been proven to be safer with more favorable outcomes[128,134].

In addition, the response to COVID-19 vaccination is another important challenge in immunosuppressed patients. It is found that discontinuation or dose reduction of MMF optimizes the COVID-19 vaccination response in LT patients[135,136]. Moreover, it is necessary to consider booster shots in immunosuppressed patients who do not demonstrate the appropriate response to vaccinations[137]. On the other hand, pre-exposure prophylaxis with tixagevimab/cilgavima can be beneficial in LT patients with severe immunosuppression who did not respond adequately to COVID-19 vaccination or COVID-19 vaccine contraindication[138]. The humoral response to COVID-19 vaccines is 66% for patients with LT[120]. Luo *et al*[120] also revealed that the worse humoral response to COVID-19 vaccinations in LT patients was observed in patients with a history of using MMF (OR: 3.27, 95%CI: 1.45-7.41), diabetes (OR: 2.75, 95%CI: 1.48-5.09), and the use of > 2 immunosuppressive drugs (OR: 3.13, 95%CI: 1.22-7.99).

Transplant candidates waiting for a donor are also considered high-risk due to their underlying liver disease. COVID-19 can complicate the LT process as an affected patient cannot undergo transplant surgery until declared recovered from COVID-19. It is suggested that the transplant should be performed with one negative COVID-19 reverse transcription-PCR test 24 h prior to the transplantation [139]. It was found that COVID-19 infection before liver transplantation in patients with high MELD scores was not associated with a higher mortality rate[140]. As a result, postponing the surgery to a later time than what is suggested above is not recommended.

Nonalcoholic fatty liver disease

NAFLD is a liver manifestation of metabolic syndrome and is the most common CLD all over the world, affecting 30%-40% of the world population[141,142]. The spectrum of NAFLD ranges from hepatocellular steatosis to advanced liver cirrhosis[143]. There was a great heterogeneity across different studies which assessed the severity outcomes of COVID-19 in patients with NAFLD[144-147]. Two meta-analyses suggested a more severe disease course and higher rates of ICU admission in NAFLD patients[92,148].

MAFLD is a more recent term to describe fatty liver disease in the context of metabolic syndrome [142]. It is considered a better reflection of the disease pathogenesis and can contribute to a more appropriate disease classification and management. NAFLD patients were diagnosed and included in the studies mainly based on their imaging (computed tomography or sonography) findings; however, metabolic risk abnormalities should be considered beside the imaging findings of hepatic steatosis to label a patient as MAFLD[149]. The existence of MAFLD can lead to the release of more inflammatory cytokines and worsens the inflammatory process in COVID-19 infected patients[150]. Gao *et al*[151] found that the elevated level of IL-6 was associated with poorer COVID-19 outcomes in MAFLD patients. Leptin dysregulation in metabolic syndrome and obesity can be responsible for the more prominent cytokine storm observed in these conditions[152]. Therefore, it seems that metabolic syndrome features which are incorporated in the definition of MAFLD are the determinants of the disease severity in patients with fatty liver. This also clarifies the inconsistency of the results about disease severity in NAFLD patients with COVID-19, but a more consistent result for MAFLD that we described above.

Another predictor of disease severity is the degree of NAFLD or MAFLD and liver fibrosis. Targher *et al*[146] found that MAFLD patients with intermediate to high fibrosis-4 (FIB-4) scores had poorer COVID-19 outcomes (OR for intermediate FIB-4 = 4.32, 95%CI: 1.94-9.59; OR for high FIB-4 = 5.73, 95%CI: 1.84-17.9). Another study found that the increase in various liver fibrosis scores, including FIB-4, aspartate aminotransferase to platelet ratio index, NAFLD fibrosis score, and Forns scores was associated with worse COVID-19 outcomes and, as a result, can be used as prognostic factors[153]. However, their accuracy in identifying liver fibrosis is not acceptable in young individuals and both extremes of body mass index[154,155].

Pregnancy

The presence of liver involvement can partially impact COVID-19 prognosis in pregnant patients. It is shown that the duration of admission in COVID-19 pregnant females is more prolonged in those with liver involvement[156]. Moreover, pregnant females with liver injury are at higher risk of developing severe disease[157]. Nevertheless, their neonates do not have an excessive risk for worsening prognosis.

The prevalence of COVID-19-related liver injury in pregnant women is nearly 30%, which is relatively similar to the general population[157]. The first step in managing a pregnant patient who presents with COVID-19 and liver injury is to identify the cause of liver damage and exclude obstetric diagnoses. COVID-19-related liver involvement can be mistaken for preeclampsia[158], HELLP syndrome[159], acute fatty liver of pregnancy[158], and intrahepatic cholestasis[160]. All these conditions warrant early diagnosis and require certain urgent management. Therefore, it is highly recommended to monitor liver function tests in pregnant females[157].

Myalgia is one of the most common presentations of COVID-19, which is usually managed with acetaminophen plus non-steroidal anti-inflammatory drugs (NSAID)[161]. As the use of high-dose NSAID is not recommended during pregnancy, especially during the third trimester, higher doses of acetaminophen might be prescribed to control the pain, which might exacerbate the underlying liver disease. Therefore, physicians should calculate the safe dose of acetaminophen to prevent the exacerbation of underlying liver disease[162].

Infants and children

Severe COVID-19 disease in adults is linked to dysfunctional cellular immunity and unchecked inflammatory cytokines production[163]. The unaffected immunosuppressive and cellular elements of the immune system in children can result in a less aggressive course of COVID-19. This milder course of COVID-19 can explain the lower rate of elevated AST and ALT in children (6%-22%)[164,165], compared to adults (14%-53%)[166]. The most common hepatic presentation of COVID-19 is the elevation of liver enzymes. Elevated ALT is usually seen in older male children[167]. Supportive treatment is generally considered for managing COVID-19-affected children with liver involvement.

In addition to COVID-19-related liver injury, pediatricians should be aware of the management of COVID-19 in children with pre-existing liver disease. It was revealed that the severity of COVID-19 was not higher in children with CLD[168]. Therefore, children with stable CLD can be managed virtually with a well-organized telemedicine system. Similar to adults, in children with autoimmune liver disease or LT, who are receiving immunosuppressive drugs, it is not recommended to decrease the dose of drugs in mild cases, as it can increase the chance of organ rejection[163].

Neonates can be affected by COVID-19 *via* three routes: antenatal, peripartum, and postnatal. Liver involvement in neonates is mainly characterized by elevated liver enzymes. In these cases, the first step

is to exclude other causes of abnormal liver function tests[169]. Remdesivir should be administered in neonates with COVID-19 with great caution and only in severe cases as it can worsen liver injury in COVID-19- infected neonates[170].

EPIDEMIOLOGICAL ASPECTS OF LIVER DISEASE DURING THE COVID-19 PANDEMIC

COVID-19 can cause liver injury *via* different mechanisms discussed above. In addition to these mechanisms, the COVID-19 pandemic contributed to some changes in the pattern and epidemiology of some of the hepatic diseases.

Alcoholic liver disease

The amount of alcohol consumption and prevalence of alcoholic liver disease have risen during the COVID-19 pandemic. Several reports from different countries worldwide demonstrated a significant rise in the amount of alcohol use during the pandemic, including the United States[171], China[172], and England[173]. It is postulated that this increase resulted from financial problems, job loss, and mental distress during the pandemic[174-176]. Besides, the psychological impacts of the loss of beloved ones, social isolation, lockdown, and other mitigation strategies that were implemented to control the disease have resulted in a greater level of mental distress and, as a result, aggravated alcohol use even more [177-179]. Therefore, it was expected to observe higher rates of alcoholic liver diseases and their burden. Numerous reports from across the globe provided data regarding the increased burden, hospitalization, and mortality due to excessive alcohol consumption during the pandemic. A study from Canada found that the rates of monthly hospitalization due to alcoholic hepatitis increased from 11.6 before March 2020 to 22.1 cases *per* 10000 amid the pandemic, which indicates a nearly two-fold increase in the number of cases[180]. A similar increase rate was also observed in another study from England[181]. Two reports from the United States suggested a nearly 50% increase in the case admission due to alcoholic hepatitis during the pandemic[182,183]. In concordance with the increase in case hospitalization, we also observed a 20% rise in mortality rates due to alcoholic hepatitis[184]. Females and younger individuals are more likely to experience these increasing trends in hospitalization and mortality rates due to alcoholic liver disease[183,184]. Several strategies can be implemented to mitigate the detrimental effects of the COVID-19 pandemic on patients with alcohol use disorders. Developing a well-organized telemedicine system can help better identification of high-risk persons and provide consultation, health-related suggestions, and surveillance[179]. The screening programs can also be used for earlier identification of at-risk groups for alcohol use disorder. Alcohol Use Disorders Identification Test – Consumption and Single Alcohol Screening Question are two recommended screening tools for assessing alcohol use disorder and are suggested to be used for all persons over 18 during primary care evaluation[185,186].

Hepatitis B virus

In addition to alcoholic liver disease, HBV infection is another hepatic disease which is affected by the COVID-19 pandemic. Implementation of the strategies to mitigate the spread of the pandemic, including the lockdown, resulted in more difficult access to the healthcare facilities and, thus, reduced the willingness of many patients to seek medical services[187]. As a result, the number of HBV tests was reduced, and HBV diagnosis and treatment were impacted negatively amid the pandemic[188]. In addition, there are reports which indicate that the failure of the screening programs lowers the number of HBV vaccination and aggravates the preexisting health inequalities during the pandemic[188,189]. All these can contribute to a notable rise in the number of HBV cases. Similar to what we proposed to tackle the burden associated with the alcoholic liver disease during the pandemic, telemedicine and remote screening programs can be useful to resolve the pandemic-related disruptions in HBV infection management. Also, integrating the messaging system and contact tracing into the screening programs is suggested to increase the efficacy of screening; however, their effectiveness is yet to be determined by future studies[190].

CONCLUSION

Liver injury is a relatively common manifestation of COVID-19, mostly presenting with elevated liver enzymes. Different mechanisms for COVID-19-induced liver injury, including direct viral effect, cytokine storm, hepatic congestion, hypoxia, and reperfusion injury are proposed. Most cases of liver injury are mild and only require supportive treatment; however, there are some underlying liver diseases which might require special considerations. NAFLD and MAFLD were associated with the highest OR for severe COVID-19. Also, more severe disease is expected in patients with liver cirrhosis, especially cases with more advanced liver fibrosis. Despite the immunocompromised status in LT and AIH patients, they are not at a significantly higher risk of severe disease, and there is no need to

empirically reduce or change the immunosuppressive drugs.

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Abstract

Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer, accounting for 75%-85% of cases. Although treatments are given to cure early-stage HCC, up to 50%-70% of individuals may experience a relapse of the illness in the liver after 5 years. Research on the fundamental treatment modalities for recurrent HCC is moving significantly further. The precise selection of individuals for therapy strategies with established survival advantages is crucial to ensuring better outcomes. These strategies aim to minimize substantial morbidity, support good life quality, and enhance survival for patients with recurrent HCC. For individuals with recurring HCC after curative treatment, no approved therapeutic regimen is currently available. A recent study presented novel approaches, like immunotherapy and antiviral medication, to improve the prognosis of patients with recurring HCC with the apparent lack of data to guide the clinical treatment. The data supporting several neoadjuvant and adjuvant therapies for patients with recurring HCC are outlined in this review. We also discuss the potential for future clinical and translational investigations.

Key Words: Recurrent hepatocellular carcinoma; Liver transplantation; Therapy; Immunotherapy; Neoadjuvant and adjuvant therapy

Core Tip: Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer, and up to 50%-70% of individuals may experience a relapse of the illness in the liver after 5 years. This review will provide novel approaches to improve the prognosis of patients with recurring HCC with the apparent lack of data to guide the clinical treatment. Neoadjuvant and/or adjuvant therapy methods potentially elevate the opportunity of cure in refractory patients with recurrent HCC and contribute to a better long-term prognosis.

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INTRODUCTION

With an expected 906000 new cases and over 800000 fatalities, primary liver cancer is ranked as the sixth most commonly diagnosed malignancy and the third most prevalent cause of cancer-related deaths worldwide in 2020[1]. Hepatocellular carcinoma (HCC) accounts for 75%-85% of cases of primary liver cancer[2]. As medical care has improved, liver transplantation (LT) has emerged as the best option for individuals with HCC that is either incurable or who have progressive liver damage as a result of their HCC[3]. Although patients receive treatments for early stage HCC intending to cure the disease, up to 50%-70% of patients may experience disease relapse in the liver after 5 years[4,5]. This is not only related to the inadequacy of the surgery (*i.e.*, positive surgical margin) but is also frequently associated with the development of *de novo* tumors as the disease progresses. Additionally, 70% of patients with recurrent HCC experience an early relapse within 2 years of surgery, which is nearly incurable and has been linked to apoor prognosis[6]. The molecular mechanisms underlying the prompt relapse of HCC are still unclear.

In a small percentage of HCC patients with multifocal intra or extrahepatic relapse, liver function impairment, and tumors that cannot be removed, rehepatectomy is necessary[7]. According to reports, HCC patients with tumors that meet the Milan criteria had excellent 5-year survival rates and minimal risks of relapse after LT[8]. Until the disease worsened or tolerance was established, monotherapy was thought to be the only course of therapy. At least two treatments administered simultaneously or within 4 wk of each other were considered multimodal therapy[9]. Preclinical findings suggest that neoadjuvant and adjuvant dosages should be used in combination instead of using either of them individually[10].

Therefore, it is crucial to devise the best treatment plans and fully comprehend the mechanism of HCC relapse. As a result of these problems, numerous researchers have looked into the benefits of neoadjuvant and adjuvant therapeutic approaches to lower relapse rates and enhance prognosis. Adjuvant therapy is not typically advised following curative treatment since its benefits are unclear[11]. It is clear that some additional treatment modalities are necessary, and in this regard, either neoadjuvant or adjuvant approaches are mostly taken into consideration. These include adjuvant antiviral therapy, repeated excision, transarterial chemoembolization (TACE), transarterial radioembolization, radiofrequency ablation (RFA), LT, tyrosine kinase inhibitors, and immunotherapy. Here, we will discuss the current state of knowledge on and recent advances in the therapy of recurrent HCC in this narrative review.

MECHAMISM OF RECURRENT HCC

Up to 70% of early HCC recurrence cases were thought to manifest within the first two years following curative therapy; relapses that occur after this point are referred to as late HCC recurrences[12]. Malignant, immunological, and stromal cells are made up of heterogeneous cell types that interact spatiotemporally in complex tumor ecosystems[13]. Recent research has found similarities between the genetic variants of primary and early recurrent HCC[14]. Nevertheless, explanations for differences between the cellular ecosystems of primary and recurrent HCC are still being sought after. Early-relapse HCC displayed decreased regulatory T cells (Tregs) and higher dendritic cells (DCs) and CD8+ T cells compared to primary HCC, which were associated with a poor prognosis[15], as shown in Figure 1. Treg recruitment is a characteristic of the immunosuppressive milieu of primary HCC[16]. In contrast to the traditional depletion state in primary HCC, CD8+ T cells in relapsed HCC displayed higher CD161

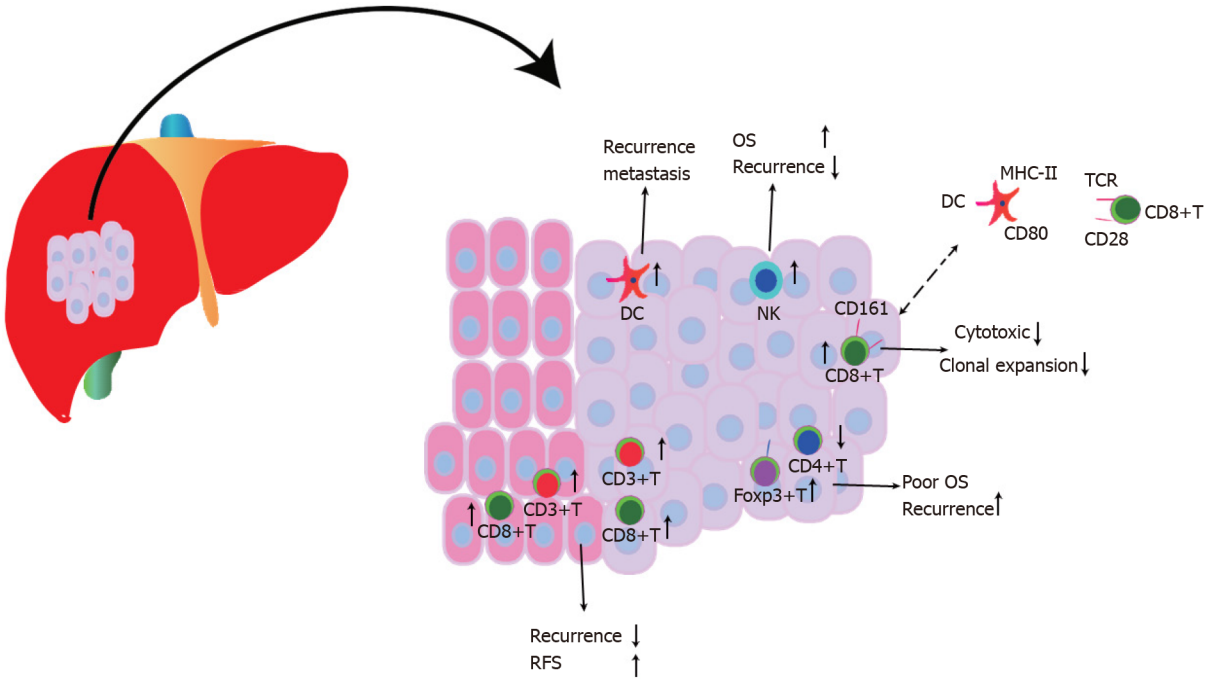

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Figure 1 Mechanism of action of immune cells under investigation for recurrence of hepatocellular carcinoma. Early-relapse hepatocellular carcinoma displays decreased regulatory T cells, and higher dendritic cells and CD8+T cells. FoxP3(+) regulatory T cells encourage a gradual decline in CD4+ cytotoxic T cells, which contributes to poorer survival and high recurrence rates. OS: Overall survival; RFS: Relapse-free survival; DC: Dendritic cells; NK: Natural killer cell.

expression, a low cytotoxic state that was innate, and reduced clonal expansion. This is significant because the immune escape mechanism underlying HCC relapse was connected to the inhibition of DC antigen presentation and infiltration of innate-like CD8+ T cells[15], which caused intrahepatic dissemination of HCC. Tregs and intragraft Toll-like receptor 4/C-X-C motif chemokine 10/CXCR3 C-X-C motif chemokine receptor 3 levels were higher in patients with HCC recurrence following LT, which was further substantiated in a rat transplantation model[17].

According to a meta-analysis, HCC patients with high Foxp3+ T cell infiltration had worse 1-, 3-, and 5-year survival rates and a greater rate of recurrence than patients with low Foxp3+ T cell infiltration [18]. The frequency of CD8+ tumor-infiltrating lymphocytes in the intratumor and margin area was positively correlated with overall survival (OS) and disease-free survival (DFS) in two HCC cohorts (a combined total of 449), and a larger proportion of CD8+ tumor-infiltrating lymphocytes was associated with a lower recurrence rate[19]. As a result of their inflammatory condition, increased densities of CD8+T lymphocytes that infiltrate the liver in HCC patients contribute to tumor recurrence and carcinogenesis[20]. High CD3+ and CD8+ T cell densities were associated with minimal relapse and extended relapse-free survival in both the tumor center and margin[21]. In HCC patients, increased FoxP3(+) regulatory T cells encouraged a gradual decline in CD4+ cytotoxic T cells, which contributed to poorer survival and high recurrence rates[22]. A high Foxp3/CD8 ratio indicated a higher Edmondson-Steiner nuclear grade, relapse, and shorter OS and DFS, along with worse differentiation[23]. In HCC patients who received LT but not Foxp3+ T-lymphocytes, a correlation between CD4/CD8 ratio and tumor recurrence was established[24]. After surgical excision, high DC infiltration in HCC nodules can be used as a predictor of the recurrence and metastasis of the disease[25]. The response to sorafenib improved relapse-free survival, and OS in patients was significantly influenced by the increased density of natural killer (NK) cells[26].

In HCC patients after surgery, higher interleukin (IL-11) levels enhanced tumor expansion, and in genetic mouse model, suppression of IL-11-STAT3 signaling greatly reduced cell proliferation and post-surgical recurrences of HCC tumors[27]. Local recurrence is caused by the invasion of local tumor blood flow and peritumoral diffusion, whereas systemic dissemination is caused by the "rehoming" of circulating tumor cells that have spread from the initial nodules[28]. HCC recurrence can occur as a result of tumor cells that are circulating or at rest, evading the host's immune responses. The total somatic mutations and copy number depletion of WNK2 (WNK lysine deficient protein kinase 2) were associated with low levels of WNK2 protein expression, premature tumor relapse, and poor cumulative survival in patients with HCC following curative excision, indicating a tumor-suppressor role of WNK2 [29]. WNK2 inactivation results in the recruitment of tumor-associated macrophages, ERK1/2 signaling activation, tumor growth, and metastasis.

Following therapy, HCC shows pathological modifications; therapy induced pathological variation, particularly sarcomatous transformation, results in random and frequent recurrences after RFA[30]. It is generally accepted that recurrent HCC following curative therapy was caused by both initial incomplete treatment as well as current technological and biomarker limitations that make it difficult to detect preexisting microscopic tumors[31]. Occasionally, local therapies like TACE result in the direct diffusion of tumor cells from the RFA needle, which eventually causes a relapse of HCC[32]. However, multicentric origin HCC developed from *de novo* carcinogenic effect following curative excision, and the latter has a better OS than the former[33], consistent with the results of Kuo *et al*[34]. The incidence of intrahepatic metastasis and multicentric recurrent HCC was 59.4% and 27.5%, respectively, which were accompanied by loss of heterozygosity (63.8%) and microsatellite instability (30.0%) between primary and recurrent tumors[34]. Concerning previously unidentified circulating tumor cells or preexisting metastasis caused by the current technology that contribute to extrahepatic relapse, metastatic tumor lesions in the graft are originally formed from circulating cells or extrahepatic locales, providing a greater potential for biological advancement[35].

ADJUVANT ANTIVIRAL TREATMENT

Adjuvant antiviral therapy has been shown to decrease multicentric HCC recurrence, which in turn reduces post-treatment recurrence[33]. However, the ideal time for starting therapy with direct-acting antivirals (DAAs) for hepatitis C virus (HCV)-related HCC patients following surgical resection, and the impact of DAA on HCC recurrence remain unclear. Low risk of HCC recurrence after DAA treatment was suggested in some studies, while others have reported contrasting outcomes. Furthermore, there is conflicting evidence concerning HCV-related HCC recurrence in previously cured patients following virus elimination with DAAs. With a 5.7-mo follow-up in 20 DAA-treated HCV patients, a high rate of early HCV-related HCC recurrence was observed[36]. Even though DAA treatment was not associated with HCC or early HCC recurrence, a higher proportion of DAA-treated patients accepted potential curative therapy for recurrent HCV-related HCC compared to untreated patients (32.0% *vs* 24.6%) and developed a non-significant complete or partial response (45.3% *vs* 41.0%)[37]. A systematic review has highlighted an association of HCC recurrence with the status of previous HCC recurrences and the shorter interval between HCV-related HCC complete response and initiation of DAA treatment, and similar recurrences in patients treated with DAAs, those treated with interferon, or untreated patients [38]. HCV-related HCC patients, who had a shorter interval between HCC treatment and DAA therapy (less than 4 mo), appeared to be at greater risk, with a relapse rate of 41.2%[39]. DAA treatment following curative HCC therapy was not associated with early or advanced cancer recurrence[40]. DAA treatment is not associated with a high risk of recurrence in LT patients with HCV and HCC who achieved an original complete response to local-regional therapy, but rather involves a low risk of waitlist dropout due to cancer aggression or death[41]. In three separate prospective cohorts, no increased risk of HCC recurrence following DAA therapy was found, particularly in patients who received curative treatment, such as LT[42].

Even though the impact of DAAs on HCV-related HCC recurrence remains debatable, the results of anti-hepatitis B virus (HBV) treatment following HCC therapy showed that NAs might potentially inhibit HCC recurrence after curative hepatectomy in patients with HBV-related HCC[43]. Managing viral conditions and reactivation of viral replication plays a major role in suppressing HCC recurrence, maintaining liver function, and improving survival for HBV-related HCC post-therapy[44]. After curative therapy, NAs significantly improved recurrence-free survival and OS in HBV-related HCC patients, and entecavir was on par with other NAs, including lamivudine and adefovir, in this regard [45]. Another study discovered that after curative therapy, antiviral therapy with NA could increase survival and reduce early recurrence in patients with HBV-related HCC[46]. NA with or without anti-HBs immunoglobulins was significantly effective in inhibiting post-LT HBV recurrence[47]. In a limited sample cohort, NA did not lower the short-term recurrence rate but increased the elimination of postoperative serum HBV and remnant liver volume, which resulted in significantly improved tolerance to follow-up treatment for HCC recurrence[48]. In a large cohort of 4569 patients with HBV-related HCC who underwent curative resection, the anti-HBV therapy cohort had a significantly lower 6-year HCC recurrence rate than the control cohort [anti-HBV therapy, 45.6%; 95% confidence interval (CI): 36.5%-54.6% *vs* control, 54.6%; 95%CI: 52.5%-56.6%][49]. According to a previous study, recipients who accepted LT by removing HBV-infected initial liver at undetected serum HBV DNA levels continue to have an elevated risk for posttransplant recurrent HBV due to the absence of any particular treatment [50]. In comparison to lamivudine for HCC after curative therapy, entecavir is associated with a four-fold higher one-year OS rate and lower HCC recurrence, suggesting that entecavir may be more suitable for HBV-related HCC patients[51].

REPEAT RESECTION

Only a small proportion of patients with recurrent HCC are candidates for repeat hepatectomy due to recurrent multifocal tumors and compromised liver function[52]. Twenty-two patients with recurrent HCC following LT (2 intrahepatic HCC patients and 20 extrahepatic HCC patients) received complete hepatectomy and had a longer median survival of 35 mo than unresected patients with a median survival of 15 mo[53], suggesting a less aggressive tumor biology. According to a retrospective cohort study, 15 patients with HCC recurrence who underwent LT had a better 5-year OS rate and 5-year DFS rate than the patients with RFA treatment (35% *vs* 28%, and 16% *vs* 0%, respectively)[54]. A recent study reported that repeat laparoscopic liver resection (LR) for recurrent HCC is both feasible and suitable with promising short-term results[55]. Laparoscopic repeat LR was associated with shorter hospitalization and prolonged operation time compared to open repeat LR for recurrent HCC but they had similar perioperative results for primary HCC except for a longer operation time[56]. Patients who underwent wedge resection during laparoscopic repeat LR showed a significantly lower postoperative complication rate than open repeat LR (7.2% *vs* 21.8%)[57]. Even though patients with open LR have a higher morbidity rate than those who underwent LR for primary HCC, there are no striking differences in the clinical characteristics of repeat laparoscopic LR based on prior resection method (open or laparoscopic) or tumor location (segments 7 and 8 or other)[55].

A meta-analysis of 767 patients, 334 of who had repeat laparoscopic hepatectomy and 433 of whom had repeat open hepatectomy, discovered that repeat laparoscopic hepatectomy resulted in less intraoperative blood loss, fewer major complications, shortened hospitalization, and a higher rate of R0 resection[58]. The repeat-surgery group had better liver function, long recurrence-free survival (16.5 mo *vs* 11.4 mo), and better 5-year survival after recurrence (repeat surgery group *vs* non-surgery group: overall, 53.0% *vs* 25.7%; intrahepatic recurrence, 73.8% *vs* 37.2%; extrahepatic recurrence, 30.0% *vs* 0%; intrahepatic and extrahepatic recurrence, 34.1% *vs* 10.6%) compared to the non-surgery group[59] for recurrent HCC. Patients with recurrences within 6 mo of resection had poor survival outcomes than those who experienced recurrences later, and patients with intrahepatic-only recurrences had a better prognosis than those with either extrahepatic-only or intra and extrahepatic recurrences[60]. Additionally, repeated resection of recurrences with a remediable objective produced better outcomes than other therapy options[60]. After 18 mo of initial hepatectomy, repeat hepatectomy may be suggested as a treatment for recurrent HCC. When compared to patients with intrahepatic metastasis, repeat hepatectomy improves survival rates in HCC patients with multicentric occurrence[61]. Although RFA is associated with lower grade 3 morbidity and shorter hospital stay, repeated hepatic resection resulted in a longer median recurrence-free survival *vs* RFA (23.6 mo *vs* 15.2 mo) in patients with recurrent HCC[62]. Resection can be advised as a treatment option for patients with extrahepatic recurrent HCC in conjunction with local treatment for intrahepatic recurrent HCC due to the superior outcomes[63]. At the third (71.3% *vs* 65.7%), fifth (59.9% *vs* 45.4%), and tenth (35.4% *vs* 32.2%) year follow-up, repeat hepatectomy improved long-term OS more than RFA and showed a late survival advantage for patients with recurrent HCC despite a higher morbidity rate[64].

LT

According to reports, the results of salvage LT (SLT) for recurrent HCC following hepatectomy are comparable to the outcomes of initial transplantation, even when examined on an intention-to-treat basis[65]. LT seems to be the most effective treatment for HCC patients to remove both tumors and underlying liver diseases, but the scarcity of organ donors available globally and stringent criteria for patients who are not eligible for transplantation are the major challenges. However, recurrent HCC patients following LT have a poorer prognosis, with a median OS of 10-13 mo as opposed to 2-3 years for patients who had hepatectomy[66-68]. In 2000, Majno *et al*[69] made the first suggestion for SLT, which was used in patients with recurrent HCC or liver dysfunction following primary hepatectomy as initial treatment. Fortunately, liver transplants were an option for 80% of patients with recurrent HCC following curative hepatectomy[70]. A case of salvage living donor LT in a patient with tumor recurrence following surgical resection of combined HCC and cholangiocarcinoma has multiple tumor recurrences after 21 mo due to the more aggressive tumor biology of this type of cancer[71]. The patients receiving SLT therapy demonstrated better DFS than those receiving re-resection or RFA, which is a beneficial strategy for intrahepatic recurrent HCC, particularly for patients with multicentric occurrence that is related to better long-term outcomes than the intrahepatic metastasis pattern[72].

SLT (n = 16) revealed poorer short-term perioperative results than repeat LR (n = 16), with a higher incidence of morbidity (57.8% *vs* 5.4%), reoperations (39.1% *vs* 0%), renal dysfunction (30.1% *vs* 3%), bleeding (19.8% *vs* 2.2%), prolonged intensive care unit stay (4 d *vs* 0 d), and hospitalization (19.8 d *vs* 7.1 d) but significantly decreased recurrence (15.4% *vs* 70.3%) and 5-year cumulative incidence of recurrences (19.4% *vs* 68.4%) to improve long-term survival outcomes for recurrent HCC[73]. SLT was found in a meta-analysis to have higher blood loss, longer hospital stays and surgeries, increased DFS, and elevated risk of postoperative morbidity than repeat LR, while there was no clear difference in

postoperative mortality or OS[74] for recurrent HCC. In terms of disease-specific and recurrence-free survival of patients with intrahepatic HCC recurrence, SLT with transplantable patients is superior to repeat resection, even in patients with Child-Pugh class A liver cirrhosis[75]. Only 56% of cases can be cured using the SLT strategy. A successful SLT strategy is predicted by higher end-stage liver disease scores at the start of the strategy and the absence of pre-resection TACE[76]. Even though SLT is associated with a higher rate of surgical complications, SLT for recurrent HCC following primary hepatic resection is still an efficient and safe treatment that increases survival and reduces tumor recurrence compared to patients with HCC exceeding the Milan criteria who accepted primary orthotopic LT[77]. After hepatectomy, HCC patients with larger tumor sizes were more likely to experience relapse, even with SLT. As a result, LT should be recommended as soon as possible, ideally within a year, for patients with recurrent HCC after LR, followed by meeting the requirements for transplantation[78]. For patients with recurrent HCC after hepatectomy, SLT has a poorer OS and RFS, as well as a higher risk of recurrence and death compared to primary LT, particularly for those who meet the Milan criteria[79]. Another study discovered no difference between patients receiving primary LT and SLT for HCC recurrence following primary treatment with LR or RFA in terms of the 5-year risk of recurrence and 5-year actuarial survival[80]. SLT for relapsed HCC patients after initial LR followed by SLT showed overall and recurrence-free survival rates on par with primary LT. Despite this, there are higher rates of Child-Pugh class A, more than three transplant treatments, and reoperation for postsurgical bleeding[81]. Patient background possibly has various effects on therapy, as Hong Kong patients with recurrent HCC following LR who received SLT, but not Roman patients, showed an increased recurrence rate[82].

RFA

Clinical therapy for HCC frequently involves ablation. Following ablation, the tumor experiences residual and local recurrence due to asymmetrical heat diffusion and heat absorption *via* circulating blood or air around the tumor[83]. For HCC patients who experience recurrence but cannot undergo a suitable operation, ablation is used as a safe and efficient therapy[84]. With ablation alone, the 5-year recurrence rate of HCC patients was 70%[85]. Although a small set of 11 patients with relapsing HCC following LT embraced microwave ablation without serious side effects, this safe technique still needs to be validated in larger studies or compared with other treatment options[86]. RFA and repeat resection are better choices for late-relapsing HCC patients post-curative hepatectomy who meet the Milan criteria[87]. Although the 1-, 3-, and 5-year OS (90.7%, 69.04%, and 55.6% *vs* 87.7%, 62.9%, and 38.1%, respectively) and progression-free survival (PFS) (56.5%, 27.9%, and 14.6% *vs* 50.2%, 21.9%, and 19.2%, respectively) were comparable between the RFA and repeat resection groups for locally recurrent HCC following primary resection, the former was superior to the latter in term of complications and hospitalization[88]. In a different study, repeat resection was found to increase survival for recurrent HCC, particularly for patients who had relapsed within two years and whose primary tumor burden exceeded the Milan criteria[89]. Primary HCC (94.8%, 75.7%, 61.6%, and 47.3%, respectively) and recurrent HCC (91.9%, 71.2%, 58.7%, and 45.2%, respectively) did not differ in the 1-, 3-, 5-, or 10-year OS rate[90]. RFA offers comparable long-term survival whether treatment is for the first-time or recurrent HCC that is 5 cm or less. Although LR with long-term survival results is superior to RFA for recurrent HCC patients, RFA is a good alternative to LR in patients with small-sized recurrence or patients with a limited number of recurrent nodules, even though LR has better long-term survival outcomes for patients with recurrent HCC[91]. Multiprobe stereotactic RFA as first-line therapy for recurrent HCC following LR has such low morbidity that the OS and DFS rates at 1, 3, and 5 years were 94.0%, 70.2%, and 53.3%, and 52.6%, 19.7%, and 15.8%, respectively[92]. RFA is beneficial and effective for intrahepatic recurrent HCC with 1-, 3-, and 5-year OS rates of 68.5%, 40.3%, and 40.3%, respectively, particularly for recurrent HCC following LT in the absence of finite extrahepatic metastases[93]. Due to its advantages of being less invasive, extreme selectivity, and reproducibility, RFA is suggested as a better therapy for intrahepatic HCC recurrence given that it is associated with a lower recurrence-free survival than LT[94].

In patients with recurrent HCC (tumor size < 3 cm, tumor number ≤ 2), a phase III non-inferiority trial found that the 2-, 3-, and 4-year local PFS of proton beam radiotherapy was comparable to that for RFA. However, the most common adverse outcomes were radiation pneumonitis (32.5%) and decreased leukocyte counts (23.8%) for proton beam radiotherapy, and increased alanine aminotransferase levels (96.4%) and abdominal pain (30.4%) for RFA[95], which suggested that proton beam radiotherapy was tolerable and safe with long PFS values comparable to those of RFA.

TACE

TACE is generally considered a standard therapeutic method for patients with unresectable HCC[11]. The most widely used treatment for postoperative recurrence is TACE, especially when there is a large mass or multifocal relapsed HCC[96]. The outcomes of TACE in the neoadjuvant setting are debatable.

OS showed no difference between 71 patients treated with TACE before surgery and 21 patients who underwent surgery without TACE[97]. In a retrospective study, 1457 patients were evaluated, of whom 120 were treated with preoperative TACE, and it was found that 5-year DFS was improved in patients treated with TACE[98]. Patients with primary HCC who undergo embolization have a strikingly higher chance of survival than those with recurrent HCC. A study revealed that primary HCC patients who received TACE had a median survival of 30 mo and a 29% 3-year survival rate[99]. The results of treating patients with recurrent HCC, however, showed a low median survival time of 19 mo and an 11% survival rate. Patients with primary HCC and microvascular invasion (MVI) experience recurrence after resection, and TACE treatment is more effective than resection and RFA for recurrent HCC[100]. There was no significant difference in prognostic factors or OS between the initial and recurrent TACE groups[101]. TACE was administered to 28 patients with recurrent HCC following LT; 19 of these patients (67.9%) experienced tumor-shrinking by over 25%. However, the 1-, 3-, and 5-year survival rates were lower (47.9%, 6.0%, and 0%, respectively) due to extrahepatic metastases or intrahepatic recurrences[102]. According to a different study, patients who underwent chemoembolization without experiencing any serious side effects had a significantly longer OS time following the diagnosis of HCC recurrence post-LT than those who did not receive the treatment[103]. The 1-, 3-, and 5-year OS rates did not significantly differ between the repeat resection or RFA and the TACE groups, suggesting that TACE likely was as effective as repeat resection or RFA for preventing early intrahepatic relapse following curative resection of HCC[87]. Although there is no obvious difference between RFA and TACE treatment for isolated intrahepatic recurrent HCC following LT in terms of 2-year DFS rate (20% *vs* 14%) and 4-year OS rate (33% *vs* 25%), TACE treatment seems to be more beneficial in isolated intrahepatic recurrent HCC patients following LT when RFA therapy is not suitable[104]. In contrast to TACE-alone treatment for intrahepatic recurrent HCC after hepatectomy, apatinib, a vascular endothelial growth factor receptor 2 inhibitor, in conjunction with TACE significantly improved the median PFS, short-term objective responses, and disease control rate, and had a tendency of increasing the 1- and 2-year OS rates[105]. The patients who received TACE-RFA for recurrent HCC that was less than 5 cm following LT had a higher DFS than those who received TACE alone[106]. After a follow-up of 24 mo, the median OS for patients with the first recurrence of HCC treated with multimodality therapy was 40 mo (range 8-85 mo), far exceeding that of patients with LR/ablation (27 mo, range 4-75 mo), TACE/XRT (13 mo, range 4-68 mo), and systemic treatments (26 mo, range 3-59 mo)[9].

SORAFENIB

Sorafenib, a multitarget tyrosine kinase inhibitor (TKI) and the first approved drug for HCC patients, is most frequently used as an adjuvant therapy in resected HCC patients[107] and as a frontline systemic treatment in patients with HCC recurrence after LT. However, the current data are mainly based on observational research due to the exclusion of Randomized Protocol studies and Asia-Pacific trials of sorafenib from the registered studies for HCC[107,108]. Sorafenib has a few drawbacks, including poor oral bioavailability and drug toxicities, and its OS is only marginally improved by 2.8 mo[107,109]. The impacts of sorafenib in patients with recurrent HCC who underwent an incurable liver transplant have been estimated in several retrospective studies. Based on a retrospective cohort study of 50 patients with recurrent HCC following liver transplants who initially accepted sorafenib, an objective response rate of 16% and stable disease in 50% of this population were observed, and the median OS was 18 mo[110]. Patients with HCC recurrence following LT treated with sorafenib had a better median survival of 42 mo compared to 16.2 mo for patients not receiving sorafenib, supporting the notion that sorafenib increases survival[111].

According to this study, patients with relapsed HCC have a better chance of longer OS and a better prognosis by receiving the sorafenib treatment. For patients with recurrent HCC, sorafenib-lenvatinib continuous treatment and radical resection together with nonoperative therapy were both independent favorable factors for post-recurrence survival[112]. According to Lee *et al*[113], sorafenib for recurrent HCC is associated with a better prognosis because it involves smaller intrahepatic HCC combined with favorable liver function in LT recipients, which may explain why the median OS (16.8 mo *vs* 7.1 mo) and time to development were higher in 42 HCC patients in the LT group than in 790 non-LT patients. Sequential sorafenib treatments are similarly common in recurrent HCC patients following LT. These treatments improve OS compared to non-LT treatments and do not suppress systemic treatments with concurrent antirejection strategy[35]. Treatment with sorafenib and TACE was associated with a higher 5-year OS and PFS compared to those treated with TACE alone in patients with recurrent intermediate-stage HCC and lesions positive for MVI, but patients with MVI-negative lesions did not show a survival benefit from combined therapy[114]. Treatment with sorafenib plus TACE improves hepatic reserve, leads to a better OS, and results in longer intervals between TACE rounds in TACE-refractory patients with recurrent advanced HCC than repeated TACE treatments[115]. The RFA plus sorafenib treatment resulted in a significantly improved OS than RFA alone (1-, 3-, and 5-year OS rates of RFA-sorafenib *vs* RFA: 97.7%, 83.7%, and 54.7% *vs* 93.1%, 61.3%, and 30.9%, respectively), suggesting that adjuvant sorafenib combined with RFA was superior to RFA alone in improving survival results in patients with

recurrent HCC who meet the Milan criteria after initial LT[116]. Prussian blue (PB) nanomaterial is safe and has multiple roles as an antidote to thallium poisoning[83]. With minimal injury to surrounding healthy tissues, photothermal therapy is a highly effective and noninvasive therapeutic option[117]. By using human and mouse HCC cell lines, Zhou *et al*[118] developed HCC-targeted SP94 peptide and cyanine (Cy) 5.5-conjugated PB nanoparticles loaded with sorafenib for HCC-targeted multimodality imaging and combined photothermal therapy/sorafenib treatment. These nanoparticles accumulated in HCC tumor sites and then controlled the release of sorafenib to eradicate the tumor without any local recurrence and with a minimal amount of toxic side effects.

OTHER TKIS

The United States and Europe approved lenvatinib in the first line, cabozantinib, and ramucirumab in the second line as a potential systemic therapeutic approach for liver transplant recipients with relapsed HCC. A retrospective multicenter study discovered that regorafenib, a multitarget TKI, was safe and effective for patients with recurrent HCC following LT who were tolerable to sorafenib, with a median OS of 12.9 mo[119]. Lenvatinib, as a TKI, has been used as an optional frontline treatment strategy. Patients with recurrent HCC treated with lenvatinib who are tolerable to sorafenib have a longer median OS (19.5 mo), far exceeding those who are receiving intermittent sorafenib or regorafenib following sorafenib failure (12 mo)[112]. Cabozantinib, a TKI of vascular endothelial growth factor receptor 2 (VEGFR2), is used as an effective and safe monotherapy to proceed with third-line systemic therapies in advanced HCC[120]. Patients with recurrent HCC who received lenvatinib treatment had decreased expression of programmed death ligand 1 (PD-L1) and Treg infiltration in the tumor compared to the matched primary tumor, suggesting that lenvatinib targets fibroblast growth factor receptor 4 to increase the antitumor immune response of anti-programmed cell death-1 (PD-1) treatment, which is accompanied by decreased expression of tumor PD-L1 and Treg infiltration[121]. As a multi-kinase inhibitor, cabozantinib is expected to be an effective treatment for advanced HCC patients with sorafenib tolerance[122]. A case study identified a patient with recurrent HCC who had more than 10 years of survival after receiving an intensive multimodal therapeutic strategy that included surgery, RFA, and systemic therapy with cabozantinib as the second-line therapy in living-donor LT[123]. In patients with HCC recurrence following LT with sorafenib tolerance, regorafenib treatment resulted in a longer median OS (28.8 mo) than best supportive care (15.3 mo). This makes regorafenib a safe and effective second-line treatment option[124].

IMMUNE CHECKPOINT INHIBITORS

Although the importance of immune evasion in the progression of HCC recurrence was widely acknowledged, the lack of effective medications to reverse cancer-related immune suppression remained an untreatable condition until recently. Programmed cell death receptors on T cells and their ligands PDL-1 and PDL-2 on tumor cells are the targets of immune checkpoint inhibitors (ICPIs). Only 15–20% of patients benefit from anti-PD-L1 monoclonal antibodies (mAbs), which block interactions with PD-1 and PD-L1 and restore the roles of T cells in the tumor microenvironment[125,126]. Stimulation-induced immune surveillance has notable antitumoral outcomes in advanced and recurrent HCC, with significant response rates and even complete responses. Despite their promising prospects, ICPIs must be used with caution in transplant patients due to the complexity of HCC. In particular, HCC patients with multifocal tumors, higher AFP levels, larger tumor volume, and poorer differentiation presented a high risk of post-LT relapse when given neoadjuvant ICPIs[127]. The perioperative nivolumab *vs* ipilimumab/nivolumab combination had fine effects, according to a phase II study, with a 29% complete response rate[128]. The immune checkpoint blockade remedy resulted in only 16%-20% response rates among patients with advanced HCC[129]. Combination therapy with anti-PD-1 plus RFA for recurrent HCC achieved a superior recurrence-free survival compared to RFA monotherapy[130]. By combining anti-PD-L1 mAb with SP94-PB-sorafenib-Cy5.5 nanoparticles plus near-infrared therapy, Zhou *et al*[118] also observed the production of extraordinary results, such as suppression of distant metastases and obstruction of cancer relapse. Note that, different from primary HCC, the therapeutic strategy for recurrent HCC following LT has to be discrete due to the higher risk of allograft rejection or graft loss[131,132]. For early HCC recurrence after radical resection, TKIs combined with PD-1 therapy demonstrated a better survival benefit than TKIs alone[133]. In a patient with recurrent, refractory, metastatic HCC following LT, PD-1 inhibitor eliminated lung metastases and resulted in a partial radiological response of metastatic retroperitoneal lymph nodes after 13 cycles[134].

HBV-SPECIFIC T-CELL IMMUNOTHERAPY

Chimeric or classical T-cell receptors (TCRs)-redirected T cells target HBV antigens/epitopes expressed on HBV-infected hepatocytes or in HCC cells as an immunotherapeutic approach. According to a case study, the HBV antigen was expressed in the metastases of a patient with HBV-related HCC after LT [135]. To treat extrahepatic metastases of chemotherapy resistance, HCC autologous T cells were genetically redirected to express an HBsAg-specific T cell receptor. This resulted in decreased HBsAg levels without worsening liver inflammation or other toxicity[135]. In two patients with metastatic recurrence of HBV-related HCC after LT, immunotherapy of HBV-specific TCRs was safe and did not cause any damage to liver function over a year[136]. Notably, a patient appeared to have a reduced volume in 5 of 6 pulmonary metastases during the first year of T-cell management[136]. HBV-specific TCR T-cells transiently escape the immunosuppressive effects of tacrolimus and mycophenolate mofetil owing to the activation of CD39+ Ki67+ peripheral blood mononuclear cells, which are positively correlated to clinical outcomes in patients with HBV-related HCC relapses following LT[137].

OTHER IMMUNOTHERAPIES

Cytokine-induced killing (CIK) cell-based immunotherapy has gained popularity as a promising new adjuvant therapy approach. CIK cells are a mixture of T lymphocytes, which are *ex vivo* amplified with cytokines and comprised of CD3+/CD56+ and CD3+/CD56- T cells, as well as CD3-/CD56+ NK cells, which have potent antitumor activity with the combined ability of both T cells and NK cells and minimal cytotoxicity to normal cells, but tremendous specificity to cancer cells[138]. Multiple clinical trials revealed that CIK cell-based immunotherapy increased RFS in HCC patients who underwent surgical resection[139,140]. The production of an individual autologous CIK cell-based immunotherapeutic agent involves activating peripheral blood mononuclear cells from the relevant patients with IL-2 and anti-CD3 antibodies[141]. According to research by Lee *et al*[141], the average RFS for HCC patients who accepted the CIK cell-based agent after curative therapy was 44.0 mo, as opposed to 30.0 mo for those who did not receive adjuvant immunotherapy. The results of a meta-analysis reported that the results of DC-based immunotherapy increased antitumor immunity, enhanced survival rate, and improved survival times in HCC patients[142]. Another meta-analysis listed 22 distinct studies with 3756 HCC patients that received DC-based vaccine and/or CIK-based adoptive therapy after receiving different HCC interventional therapies. These studies showed a prolonged OS (6 mo, 1, 3, and 5 years) and reduced mortality and recurrence at 1, 2, and 3 years but not 5 years[143]. For HCC patients, a personalized neoantigen vaccine served as a safe, practical, and effective anti-recurrence treatment [144]. After a radical operation on seven postoperative HCC patients who had received all of the planned neoantigen vaccinations, five of them showed neoantigen-activated cell responses and longer RFS than the other five patients, who had only received primary vaccination and had propensity scores that matched with those of control patients[144]. After curative resection or RFA in the first stage, the personalized neoantigen-loaded DC vaccine and neoantigen-activated T-cell therapy were successfully used on ten patients with HCC without unexpected delay or grade 3 therapy-related side effects[145]. New circulating multiclonal neoantigen-specific T-cell responses, activated neoantigen-specific immunity, an upregulated immune stimulatory signature, increased immune-cell infiltration, and elevated T-cell inflammatory gene expression, were produced in 70% of patients who had improved DFS compared to non-responders, and 71.4% of patients were without relapse for 2 years after curative treatment. Neoantigen depletion (immunoediting) also increased in recurrent tumors compared to primary tumors, suggesting that immune evasion developed as a result of immunological therapy[145].

CONCLUSION

With its unique characteristics, recurrent HCC is still a difficult disease to treat. Every stage of the disease calls for a multidisciplinary approach, which is still predominantly evolving. LT and hepatectomy remain successful therapeutic strategies for patients with recurrent HCC. Additionally, neoadjuvant and/or adjuvant therapy techniques may improve the long-term prognosis and increase the chance of cure in refractory patients with recurrent HCC. Relying on the tumor biology and possible hepatic reserve, multimodality therapy should be used in patients with recurrent HCC. By simultaneously optimizing oncologic outcomes and minimal side effects, this therapy helps these patients have better OS and tolerability.

FOOTNOTES

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Qiao LX, and Guo XH searched the references and polished the manuscript; Yang TW and Chen DX designed the review; all authors have read and approved the final manuscript.

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REVIEW

Comparison between metabolic-associated fatty liver disease and nonalcoholic fatty liver disease: From nomenclature to clinical outcomes

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Abstract

As a result of the obesity epidemic, Nonalcoholic fatty liver disease (NAFLD) and its complications have increased among millions of people. Consequently, a group of experts recommended changing the term NAFLD to an inclusive terminology more reflective of the underlying pathogenesis; metabolic-associated fatty liver disease (MAFLD). This new term of MAFLD has its own disease epidemiology and clinical outcomes prompting efforts in studying its differences from NAFLD. This article discusses the rationale behind the nomenclature change, the main differences, and its clinical implications.

Key Words: Metabolic associated fatty liver disease; Non alcoholic fatty liver disease; Fatty liver disease; Obesity; Diabetes mellitus

Core Tip: A new nomenclature to represent the underlying pathophysiology of fatty liver disease has been created and labeled metabolic-associated fatty liver disease. This article discusses the rationale behind the nomenclature change, the main differences to nonalcoholic fatty liver disease, and its clinical implications.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a well-established terminology that was first coined by Ludwig and colleagues in 1980[1] to describe fatty liver disease arising in the absence of significant alcohol intake. Over the last four decades, there has been a rapidly growing global burden of NAFLD and its subtype nonalcoholic steatohepatitis (NASH)[2] which has a potentially progressive course that can lead to cirrhosis, hepatocellular carcinoma, liver transplantation, and potential death[3]. Currently, it is one of the most common causes of liver disease worldwide affecting nearly a quarter of the population[4,5], with increased recognition and diagnosis in younger individuals[6].

The rising body of research on NAFLD/NASH has led to a better understanding of its underlying pathophysiology and its relationship with metabolic syndrome[7]. Indeed, obesity and diabetes are the strongest risk factors associated with NAFLD/NASH. The public health and economic impacts of fatty liver disease have provoked extensive clinical trial activity targeted toward finding treatments for NASH among patients, regulators, and the biotechnology and pharmaceutical industries[8]. Despite this rapidly evolving activity, NASH resolution, and fibrosis regression rates are only 20%-30%[9].

In an effort to recognize the importance of metabolic abnormalities in an inclusive rather than an exclusive diagnosis, a group of international experts suggested a change of the name from NAFLD to metabolic-associated fatty liver disease (MAFLD)[10-12]. The criteria to diagnose MAFLD are based on evidence of hepatic steatosis in addition to one of the following three criteria: overweight/obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation. Hence, MAFLD is more reflective of the heterogeneous pathogenesis of metabolic fatty liver diseases than NAFLD.

Immediately after the reappraisal of the nomenclature, multiple studies have been carried out to better understand the epidemiologic impact of this new terminology and its differences from NAFLD. For example, in a US population-based study by Kim *et al*[13], it was found that MAFLD was associated with an increased risk of all-cause mortality after adjusting for metabolic risk factors, while NAFLD was not. Interestingly, insulin resistance and stage of fibrosis were predictors of increased liver mortality in NAFLD but not MAFLD whose liver-associated mortality is primarily driven by alcohol-associated liver disease[14]. However, an awareness of the differences between these conditions and their early recognition remains poor among general practitioners[15]. Given patients with fatty liver disease are usually asymptomatic, a high index of suspicion is required to make the diagnosis. Additionally, the clinical guidelines of MAFLD and NAFLD need to be updated on a rolling basis to keep up with the most recent management practices to prevent disease progression.

In this article, we will discuss the rationale and history behind the nomenclature change, as well as the core differences between MAFLD and NAFLD with respect to various clinical aspects in contemporary practice.

NOMENCLATURE AND HISTORY

"Fatty liver" was first described by Thomas Addison in 1836, who noted alcohol-related steatotic changes in liver histology[16,17]. A couple of decades later in 1857, George Budd noted similar histology in inactive, obese patients with a high-fat diet and alcohol intake[18]. Subsequently, Austin Flint observed a correlation between high carbohydrate intake with worsening steatosis and interval cirrhosis [19].

By the early 1900s, fatty liver changes unrelated to alcohol were well established but the mechanism of injury remained unclear. The role of diabetes as a risk factor for fatty liver began to be recognized by Pfluger in 1905 who noted an increase in hepatic steatosis in dogs who developed diabetes following total pancreatectomy[20]. These findings were later extrapolated to humans in 1936 when diet and newly discovered insulin were suggested as treatments for hepatomegaly secondary to steatosis in patients with juvenile diabetes[21].

In 1979, Adler and Schaffner developed a schema for fatty liver disease in overweight non- and light drinkers which included "fatty liver", "fatty hepatitis", "fatty fibrosis", and "fatty cirrhosis"[22]. A year later, fatty hepatitis would be designated "nonalcoholic steatohepatitis" (NASH) when Dr. Ludwig coins the term during characterizations of 20 Liver biopsies in primarily female patients with obesity and/or diabetes harboring lobular hepatitis, focal necrosis, and Mallory bodies on histology[1]. Not long after in 1986, NASH was included in the spectrum of "non-alcoholic fatty liver disease" NAFLD by Schaffner and Thaler[23,24].

Because the histology of alcohol-related and NAFLD steatosis is nearly indistinguishable from each other, NAFLD is a diagnosis of exclusion. Despite its name, NAFLD ironically includes patients with alcohol consumption of less than 14 and 7 drinks per week for men and women, respectively[25]. Further blurring the lines between NAFLD and alcoholic liver disease are studies recognizing that heavy alcohol drinkers who are obese are more likely to develop cirrhosis than non-obese heavy drinkers[25,26].

As more studies on NAFLD arose in the 21st century, NASH reappeared consistently as part of a syndrome including obesity, arterial hypertension, insulin resistance, dyslipidemia, and/or cardiovascular disease[27,28]. To better capture this syndrome, terms like "metabolic syndrome", "Syndrome X", "Insulin Resistance syndrome", and "the deadly quartet" were used[29]. The need for a more unified definition was reiterated in 2005, considering that the name "NAFLD" in no way highlighted the underlying metabolic etiologies, associated risk factors, or the phenotypic heterogeneity of the disease[30]. This paved the way for the introduction of the term "metabolic-associated fatty liver disease" in 2011 and was subsequently adopted in 2020 by international consensus[10,12]. Whereas NAFLD is defined as the presence of steatosis in > 5% of hepatocytes in the absence of other liver disease etiologies, MAFLD is defined by hepatic steatosis and components of the metabolic syndrome. MAFLD recognizes the positive determinants of the disease rather than defining the disease as the absence of other diseases, akin to the transition from “Non-Hepatitis A/Hepatitis B” to formally recognizing that entity as “Hepatitis C”[17]. Just as simultaneous alcohol-related liver disease and viral hepatitis can vary in disease behavior and prognosis from either entity alone, MAFLD can analogously exist with other liver diseases, including alcohol-related liver disease as patients with concomitant liver disease causes may have different outcomes than those of either disease apart[31-33].

EPIDEMIOLOGY

The adoption of the new inclusive nomenclature and diagnostic criteria for MAFLD[10] has called for multiple studies and[34-40] several meta-analyses estimating the prevalence of the disease under the new diagnostic criteria in the setting of rising numbers of patients with overweight, obesity and type 2 diabetes mellitus[41]. These studies have estimated a global prevalence of 24.2% to 39.22% for MAFLD, comprising half of the overweight and obese adults[42], compared to a 15.3% to 33.86% for NAFLD[43]. MAFLD and NAFLD patients share clinical and pathogenic features leading to similarities in their overall prevalence. However, there are differences based on the presence of other liver diseases (*i.e.*, alcoholic liver disease) that would still meet the criteria for MAFLD but not for NAFLD.

Compared to NAFLD, MAFLD is more likely to be diagnosed in Europe and Asia[44,45]. In addition, a non-statistically significant trend toward increased MAFLD in Hispanic ethnicity was reported[13]. Male sex, higher body mass index, lower high-density lipoprotein, higher triglyceride levels, and elevated aminotransferases carry a more significant correlation with MAFLD. Additionally, patients with MAFLD are more likely to have hypertension, diabetes mellitus, and chronic kidney disease[45]. Higher aminotransferases and the presence of advanced liver fibrosis in ultrasound elastography and liver biopsy are more common in patients with MAFLD+/NAFLD- when compared to a similar population with MAFLD-/NAFLD+. Mild alcohol consumption has been noted to be associated with a higher prevalence of significant fibrosis in those patients[46].

An analysis of the National Health and Nutrition Examination Survey (NHANES) database of the United States from 2017 to March 2020 found that the sample of patients with MAFLD had a higher prevalence of malignancies, coronary artery disease, myocardial infarction, heart failure, chronic pulmonary diseases, and psychiatric disorders, including sleep problems and depression when compared to the sample of patients with NAFLD; with the majority of these conditions being present in patients with more significant liver fibrosis[47].

PATHOPHYSIOLOGY AND RISK FACTORS

The exact pathophysiology of MAFLD\NAFLD remains largely unknown but a combination of genetic and environmental factors plays a crucial role (Figure 1). A contributing mechanism appears to be overnutrition and an increase in visceral adipose tissue[48]. Macrophages invade adipose tissue creating a pro-inflammatory state that promotes insulin resistance and excessive lipolysis enhancing the delivery of free fatty acids to the liver. An increased intrinsic lipogenesis overwhelms the liver's capacity to

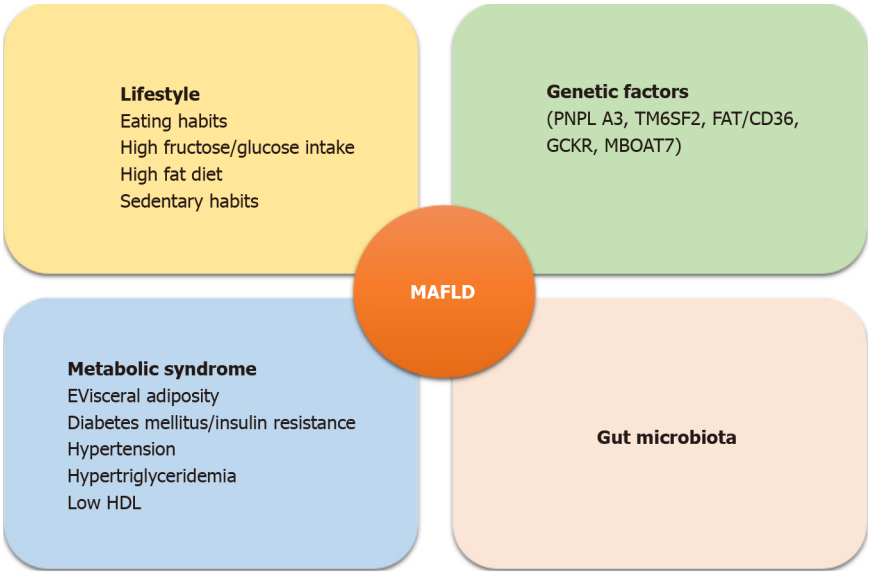

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Figure 1 Summarizes the risk factors involved in the development of metabolic-associated fatty liver disease. HDL: High-density lipoprotein; MAFLD: Metabolic-associated fatty liver disease.

metabolize fatty acids resulting in dysfunction of the hepatocytes' mitochondria and endoplasmic reticulum[49]. This dysfunction creates excessive oxidation of fatty acids and production of reactive oxygen species leading to hepatocyte death which promotes further inflammation and a vicious cycle [50].

Risk factors

Role of gut microbiota: Gut microbiotas affect pro-inflammatory and anti-inflammatory balance in the liver by their effect on gut barrier function. Increased fructose intake leads to increased permeability of enteric cells. Fructokinase is an enzyme in the liver that is also highly expressed in the gut. Metabolism of fructose by fructokinase in the intestine can result in increased permeability of enteric cells' tight junctions. This leads to increased absorption of endotoxins into the portal circulation[51]. Endotoxemia activates the innate immune system and the resulting inflammation has been shown to have a role in the transition from steatosis to steatohepatitis and cirrhosis[52] Co-occurrence of fatty liver/NASH and alteration of gut microbiota and disruption of epithelial barrier do not prove causation. The cause or consequence relationship between gut microbiota and NAFLD remains unclear. Some authors have hypothesized that liver damage might precede alteration in gut microbiota and permeability of tight junctions of enteric cells[53].

Gut microbiota also plays an important role in the metabolism of carbohydrates. Gut microbacteria can ferment dietary sugars into alcohol that can enter the portal circulation increasing oxidative stress and inflammation in the liver[54]. Studies have shown that in patients with MAFLD/NAFLD, there are significantly more gut bacteria associated with increased alcohol levels in the blood as compared to obese controls. Furthermore, some bacterial species like Escherichia, Enterobacter, Proteobacteria, and Bacteroides were found to be higher in NASH patients as compared to healthy controls[55-57].

Genetic factors: PNPLA3 (patatin-like phospholipase domain containing 3) genetic variation has been associated with MAFLD/NAFLD independent of metabolic syndrome. This gene codes for I148M that hydrolyzes triglycerides in adipose tissue resulting in increased delivery of free fatty acids to the liver [58].

TM6SF2 (transmembrane 6 superfamily member 2) encodes E167K which is a lipid transporter on the endoplasmic reticulum. Genetic variation in this protein causes loss of function and increased deposition of triglycerides in the liver[59].

Upregulation of genes coding for SREBP1c (sterol regulatory binding protein-1c), chREBP (carbohydrate responsive element binding protein), and PPAR-c (peroxisome proliferator-activated receptor gamma) results in increased *de-novo* lipo-genesis[60].

Other genes associated with MAFLD/NAFLD, and NASH are GCKR, MBOAT7, FAT/CD36, IGFBP2, PGC1alpha, SIRT1, miR-122, and miR-34. HSD17B13 appears to have a protective role[61].

Lifestyle and dietary habits

There is a close association between eating habits, obesity, and NAFLD. Increased consumption of refined carbohydrates, animal proteins, soft drinks, a high-fat diet, and fructose are closely associated

with the development of MALFD/NAFLD[51]. Carbohydrates with high glycemic index led to increased liver glycogen and fat content and increased serum triglycerides. The predominant mechanism is increased de Novo Lipogenesis[62]. Saturated fatty acids and a diet high cholesterol in diet are associated with advanced fibrosis in MAFLD.

Patients with obesity and MAFLD/NAFLD have a more sedentary lifestyle[63,64]. Finally, another modifiable factor associated with advanced fibrosis in MAFLD/NAFLD is a smoking history of > 10 pack-years although the exact mechanism is unknown[65].

HISTOPATHOLOGY OF MAFLD/NAFLD AND NASH

The presence of > 5% steatotic hepatocytes on liver biopsy is considered the minimum histologic criteria to diagnose fatty liver disease. Macrovesicular steatosis is the most common pattern although a mixed macro/microvesicular steatosis is seen in some cases as well. Pure microvesicular steatosis is not common. In MAFLD/NAFLD, small areas of lobular and portal inflammation and lipogranulomatous changes can be seen but features of hepatocyte injury and fibrosis are absent. Steatosis in adults has predilection to start in acinar zone 3 (perivenular)[66]. During the histological examination, the involvement of hepatocytes is assessed in percentages: 0%-33%-mild, 33%-66%-moderate, and > 66% hepatocyte involvement is categorized as severe steatosis[67].

On the other hand, histological features of NASH include steatosis and more severe inflammation than mentioned above along with hepatocyte injury and fibrosis. Ballooning, apoptosis, and/or necrosis are typical features of hepatocyte injury. Ballooning is of particular importance in NASH as its presence has been associated with a more aggressive disease and higher progression to cirrhosis[68]. However, the recognition of hepatocyte ballooning has significant inter-observer variation[69]. Hepatic apoptosis appears as acidophil bodies on liver biopsy. The Acidophil body index (acidophil bodies per mm^2 of tissue) serves as further confirmation of NASH when the diagnosis is uncertain.

Fibrosis in NASH typically starts in zone 3 and has a "chicken wire" pattern which entails the deposition of fibrotic material along sinusoids of zone 3 and around hepatocytes. As the disease progresses, bridging fibrosis and features of macronodular or mixed cirrhosis are seen[70]. Other histological features that may be seen in the fatty liver include megamitochondria, iron deposition, glycogenated nuclei, and Mallory-Denk bodies[71].

DIAGNOSIS

With recently published guidelines, experts have refined the criteria for the diagnosis of MAFLD. The new criterion involves the presence of hepatic steatosis in adults and the presence of one of the following: Type 2 diabetes mellitus, overweight/obesity, or metabolic dysregulation. Proposed diagnostic criteria for MAFLD are outlined in Figure 2.

Various modalities can be used to evaluate for the presence of hepatic steatosis including ultrasound, ultrasound elastography (*i.e.*, transient elastography, acoustic radiation force impulse imaging, strain elastography), computed tomography, magnetic resonance imaging (MRI), magnetic resonance spectroscopy, MRI-derived proton density fat fraction, histology and serum biomarkers (*i.e.*, fatty liver index, hepatic steatosis index, NAFLD liver fat score). Recently, ultrasound elastography has been increasingly used in clinical practice as compared to ultrasound. Ultrasound has limited sensitivity for detecting liver steatosis < 20% and performance may be suboptimal in patients with higher body mass index (BMI) > 40 kg/m^2[72-74].

Patients with normal body weight can still develop MAFLD. It was demonstrated in a recent study that patients with BMI < 23 kg/m^2 have the same disease severity on histology when compared to patients with BMI > 25 kg/m^2[75]. It is also known that metabolically unhealthy patients who are not obese and have MAFLD are at increased risk for cardiovascular morbidity and liver damage as compared to metabolically healthy individuals[76]. Moreover, hepatic fat can be an early indicator of metabolic dysfunction. Therefore, in the new criteria in addition to diabetes mellitus and overweight/obesity, patients with lean/normal weight with metabolic dysregulation are included. In these patients, the presence of at least two metabolic risk factors is needed for diagnosis. The various risks include waist circumference ≥ 102/88 cm in caucasian men and women, blood pressure ≥ 130/85 mmHg, serum triglycerides ≥ 150 mg/dL, serum high-density lipoprotein cholesterol < 40 mg/dL for men, and < 50 mg/dL for women, prediabetes, serum high-sensitivity C-reactive protein level > 2 mg/L and homeostasis model assessment of insulin resistance score ≥ 2.5. Patients who meet the criteria for MAFLD and also have one or other chronic liver condition causing fatty liver should be classified as having dual etiology (or more) fatty liver disease.

The experts have also suggested that disease severity in MAFLD should be defined by grade of activity and fibrosis stage similar to NAFLD and NASH. Patients without typical histology of steatohepatitis but have cirrhosis can be defined as MAFLD-related cirrhosis if there is past or present evidence of metabolic dysregulation risk factors for MAFLD with at least one of the following: MAFLD on a

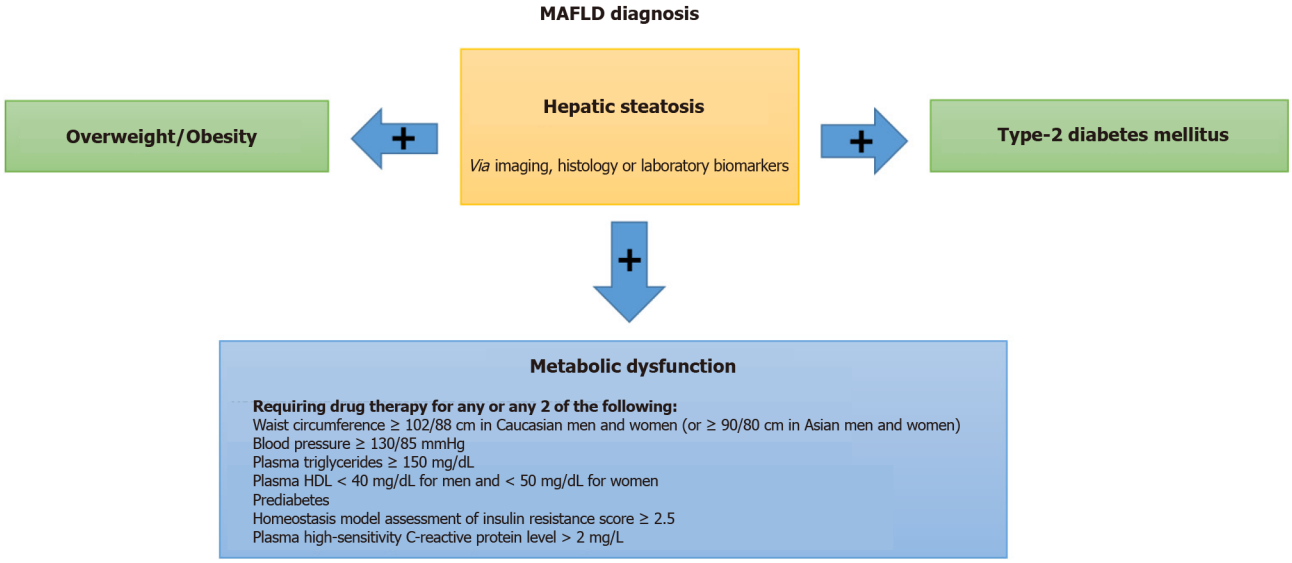

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Figure 2 Proposed diagnostic criteria for metabolic-associated fatty liver disease are outlined. MAFLD: Metabolic-associated fatty liver disease; HDL: High-density lipoprotein.

previous liver biopsy or documentation of steatosis by hepatic imaging[77].

MANAGEMENT

Despite the high worldwide prevalence, significant healthcare burden, and costs, there are currently no FDA-approved treatments for NAFLD. The 2018 AASLD practice guidelines on the treatment of NAFLD are based on the following four principles: (1) Effective diet and lifestyle modifications to achieve weight loss; (2) Identification and correction of underlying cardiometabolic risk factors; (3) Pharmacological therapy primarily aimed at improving hepatic steatosis/fibrosis; and (4) Close monitoring and prevention of complications of NAFLD[78].

Obesity and diabetes mellitus constitute the major pathophysiological risk factors for NAFLD, and drugs that modify or alter glucose metabolism and/or body weight comprise the current mainstay therapies focused on improving clinical outcomes, such as the degree of hepatic inflammation and/or fibrosis[3]. Over the past several years, multiple potential treatment options have been extensively investigated in this regard. These include insulin sensitizers and glucose-lowering drugs (such as pioglitazone, glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-glucose co-transporter-2 (SGLT-2) inhibitors), antioxidants (such as vitamin E), lipid-lowering drugs (statins), farnesoid X activated receptor (FXR) agonists and others.

The following section focuses on the different available treatment strategies for NAFLD highlighting our understanding of key elements regarding therapy.

Lifestyle modifications

Lifestyle modifications in the form of diet, exercise, and weight loss remain the cornerstone and first-line recommendation for treating patients with NAFLD/MAFLD[79]. Weight loss has by far the best evidence thus far as an independent predictor for improvement in histopathological features of NASH. The best likelihood for sustained weight loss appears to be a combination of a hypocaloric diet (decrease in caloric intake by 500-1000 kcal/d) and moderate-intensity exercise[80-82]. While weight loss of a minimum of 7%-10% of body weight is required to improve a majority of histopathological features of NASH, losing body weight by at least 3%-5% results in improved hepatic steatosis[83]. These findings were observed in a 12-mo prospective study that revealed a dose-response curve with significant improvement in histopathology with a greater degree of weight loss. Patients who achieved greater than 10% weight loss had improvement in all features of NASH, including portal inflammation and fibrosis. Importantly, patients who lost at least 5% of body weight stabilized or improved fibrosis in 94% of the cases[84]. Other lifestyle modifications may result in benefits as physical activity of more than 150 min/wk or an increase in activity level by more than 60 min/wk have been associated with a decrease in serum aminotransferases independent of weight loss[85]. On the other hand, a Mediterranean diet containing low saturated fat and high polyunsaturated and monounsaturated fats is found to be beneficial[86].

Insulin sensitizers

Pioglitazone, a peroxisome proliferator-activated receptor agonist, is a thiazolidinedione derivative that modulates glucose and lipid metabolism. It ameliorates insulin resistance in addition to creating positive effects on vascular biology, adipose tissue function, and inflammation[80]. These unique properties of pioglitazone led to immense interest among researchers in exploring its potential role in patients with NAFLD/MAFLD. A single-center clinical trial performed almost a decade ago suggested that pioglitazone at a dose of 45 mg daily in addition to a hypocaloric diet improved histological findings of steatosis, ballooning necrosis, and inflammation. However, the degree of fibrosis was no different from that of the placebo group[87,88]. More recently, in another study by Belfort *et al*[89], pioglitazone treatment not only improved the NAFLD activity score and metabolic parameters but also caused significant regression of liver fibrosis. These effects were observed after 36 mo of therapy with no significant difference in adverse events except for net weight gain of > 5.0 kg when compared to patients who did not receive pioglitazone.

Apart from the diabetic population, pioglitazone has also proven to be quite effective in NASH patients without diabetes mellitus (DM). In the Pioglitazone *vs* Vitamin E *vs* Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial, a substantially higher percentage of patients who received pioglitazone achieved resolution of NASH. However, the primary endpoint of at least ≥ 2-point improvement in NAFLD activity score did not reach predetermined statistical significance[90]. Hence, although pioglitazone is advocated for type 2 diabetes mellitus (T2DM) patients with biopsy-proven NASH, its use in the non-diabetic population still remains a debate among hepatologists.

Antioxidants

A key mechanism of hepatocellular inflammation and injury in patients with NASH is oxidative stress. Vitamin E is an antioxidant that has been investigated in multiple studies as a potential treatment option for NAFLD. Initial studies demonstrated improved steatosis and inflammation with vitamin E administration but most of these were underpowered. Furthermore, it was challenging to compare data among the available studies largely due to significant heterogeneity regarding the dose and formulation of vitamin E, inclusion criteria, and concomitant use of other antioxidants or drugs.

More recently, the PIVENS clinical trial revealed that oral a-tocopherol, administered at a dose of 800 IU/d, results in considerable improvement in liver histology at 96 wk in non-diabetic biopsy-proven NASH patients[91]. These findings are substantiated by another US-based (TONIC) clinical trial that reported a significantly higher percentage of resolution of steatohepatitis in pediatric patients with NAFLD[92]. Despite similar convincing data from a few other studies, a high dose of vitamin E has been associated with increased all-cause mortality and a higher risk of prostate cancer with no improvement in fibrosis[93,94]. As such, the general consensus at this time includes consideration of vitamin E therapy in non-diabetic NAFLD/MAFLD patients following a patient-centered individualized approach. It is currently not recommended for treating NASH patients with DM or cirrhosis.

Statins

NAFLD/MAFLD are associated with metabolic syndrome that constitutes HTN, T2DM, dyslipidemia, and obesity. Current society guidelines recommend treating associated comorbidities in NAFLD patients in addition to treating the liver disease itself. Treatment with statins was associated with lower steatosis, inflammation, and fibrosis in NASH patients[95-98]. Moreover, patients who received statins had substantially lower cardiovascular mortality without any significant liver-related adverse events. A nationwide nested case-control study from South Korea including 11593409 patients from a nationwide database suggested that statins lower the risk of occurrence of NAFLD independent of accompanying T2DM[99]. In addition to the noted benefit in reducing the incidence of NAFLD, this study also highlighted that statin usage also prevented the progression to advanced fibrosis in patients with pre-existing fatty liver disease with an adjusted odds ratio of of 0.43; 95%CI 0.42–0.44). It is therefore reasonable to initiate anti-lipid therapy for patients that meet treatment criteria. While the concern for statin-induced hepatotoxicity prevails, severe liver injury from statins is extremely rare regardless of baseline elevation of transaminases or the presence of underlying chronic liver disease.

Gastrointestinal hormones (Incretins) and newer antidiabetic agents

Glucagon-like peptide (GLP)-1 is a gut-derived incretin hormone secreted in response to oral food intake. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) constitute a novel class of well-established anti-diabetic drugs with encouraging data on the utility of these agents in treating obesity, preventing cardiovascular diseases, improving kidney function, and lowering mortality in patients with T2DM[99]. A growing body of evidence suggests that GLP-1RAs exert anti-NASH activity through several mechanisms such as increased insulin secretion, delayed gastric emptying, modulation of appetite, promoting fat redistribution, and reduced fat accumulation in the hepatocytes. A landmark UK-based 48-wk multicenter RCT (LEAN) revealed that NASH patients treated with liraglutide had a higher resolution of biopsy-proven steatohepatitis with no worsening of fibrosis when compared with placebo. Of those patients treated with liraglutide, 39% achieved resolution of NASH as opposed to only

9% in the placebo group. [Relative risk 4.3 (95%CI 1.0–17.7); P = 0.019]. These findings were supported by a Japanese pilot study (LEAN-J) where treatment with liraglutide was associated with significantly improved liver function and histological features in NASH patients with glucose intolerance[100].

Semaglutide, another GLP-1RA is currently approved for the treatment of T2DM and under extensive evaluation for weight loss[101]. Although semaglutide shares its mechanism of action with liraglutide, it has gained rapid recognition for its more pronounced metabolic effects with regard to improved glycemic control, reduced cardiovascular risk, and effective weight loss[102]. A placebo-controlled 72-wk trial suggested that once-daily subcutaneous semaglutide administered at a dose of 0.4 mg results in a higher likelihood of NASH resolution without worsening of underlying fibrosis in addition to a dose-dependent weight loss[103-105]. Despite these encouraging results, the rate of fibrosis regression was comparable between the treatment and placebo groups, and a higher number of patients treated with semaglutide experienced gastrointestinal side effects such as nausea and vomiting[106]. More refined data on histological outcomes and adverse effects will be required before the widespread use of semaglutide in routine clinical practice for the sole treatment of NAFLD/MAFLD.

Renal sodium-glucose co-transporter 2 (SGLT2) inhibitors are another class of anti-diabetic agents that work through the inhibition of glucose reabsorption in the kidneys in combination with enhanced urinary excretion of excess glucose. The consequent glucosuria results in lower blood glucose levels and eventual weight loss. A Malaysian open-label pilot study demonstrated that empagliflozin significantly improved steatosis, hepatocyte ballooning, and fibrosis in a small cohort of biopsy-proven NASH patients with T2DM. Interestingly, these effects were noted after a short duration of treatment (6 mo) and remained significant when compared with a historical placebo group at 48 wk[107]. Another meta-analysis of six randomized controlled trials including 309 patients by Xing *et al*[108] reported a positive effect of SGLT2 inhibitors in patients with NAFLD and T2DM. Patients treated with SGLT2 inhibitors achieved significant weight loss in addition to lower liver fat and improved alanine transaminase levels. Apart from the encouraging evidence on anti-NASH metabolic effects, several other studies have demonstrated improved cardiovascular outcomes in T2DM patients treated with SGLT2 inhibitors. Cardiovascular disease (CVD) currently remains the most common cause of death in patients with NAFLD, thus highlighting the added benefit of reduced cardiovascular deaths on the overall prognosis of NAFLD patients. Based on the aforementioned data, GLP-1 RAs, and SGLT2 inhibitors, either as monotherapy or combination therapy appear to be promising treatment options for NAFLD/MAFLD.

Dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin, vildagliptin, and saxagliptin; slow the inactivation of incretin hormones such as GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) by selective inhibition of DPP-4 enzymes. As such, these agents indirectly increase insulin synthesis and lower glucagon levels through the prolonged action of GLP-1. Despite the observed benefit in early studies, these drugs have failed to significantly alter the histological profile in diabetic patients with NAFLD/MAFLD[109]. Possible explanations for the lack of clinical benefit postulated thus far in the literature include non-selective inhibition of both GLP-1 and GIP enzymes that could result in counterproductive effects on weight and fatty liver, questionable need for higher dosages in human models, and short study duration (3-6 mo). DPP-4 inhibitors are currently not recommended as therapies for patients with hepatic steatosis or steatohepatitis.

FXR agonists

The Farnesoid X receptor is a ligand-activated nuclear receptor that is a key regulator for bile acid signaling and metabolism. In recent years, FXR has gained considerable interest as a potential therapeutic target for the treatment of NASH. FXR activation leads to the inhibition of bile acid synthesis and increased conjugation, transport, and excretion of bile acids. These changes ultimately result in decreased cholestasis with protection of the liver from the deleterious effect of bile accumulation[110].

Obeticholic acid (OCA), a synthetic 6α-ethyl derivative of natural human bile acid, chenodeoxycholic acid regulates lipid and glucose metabolism through stimulation and upregulation of FXR activity. The FLINT trial for the treatment of NASH revealed that OCA administered at a dose of 25 mg daily improved multiple liver histology parameters in nearly half (45%) of the patients at 72 wk follow-up [111]. These findings were noted despite the study including a significant proportion of patients with T2DM and vitamin E non-responders. This landmark study underscored the clinical relevance of FXR agonists in improving hepatic insulin sensitivity and inhibition of lipogenesis in the NASH population. These findings were later corroborated by another phase 3 study (REGENERATE) that evaluated the efficacy of OCA in 2400 patients with NASH including 2100 patients with stage 2 or 3 Liver fibrosis. This study revealed that a significantly higher proportion of patients treated with either 10 mg or 25 mg of OCA achieved regression of fibrosis compared to placebo but there was no difference between the groups in regards to complete resolution of steatohepatitis[112]. While the most common adverse event was mild to moderate pruritis, the incidence of serious adverse events was similar across the groups.

Tropifexor is a novel non-bile acid agonist of FXR that has demonstrated potent *in vivo* activity in animal models. This drug is believed to be highly efficacious in upregulating FXR target genes even at very low doses and has currently progressed into clinical development. Several phase 2 human clinical trials on the safety and efficacy of Tropifexor in patients with NASH are under evaluation[113-115].

Bariatric surgery

Weight loss through lifestyle modifications is often challenging to achieve or sustain due to the substantial need for strict adherence and patient compliance. Bariatric surgery may be opted to achieve weight loss in select patients as it helps improve lipid metabolism and inflammatory pathways involved in the pathophysiology of NAFLD. National Institute of Health consensus criteria currently recommends bariatric surgery for patients with a BMI of 35 to 39.9 kg/m^2 with any severe obesity-related comorbidity such as T2DM, HTN, NAFLD/MAFLD, and/or NASH.

A systematic review appraising 29 studies by Bower *et al*[116] showed significant improvement in several histological (steatosis, hepatocyte ballooning, lobular inflammation, and fibrosis) and biochemical parameters of NAFLD following bariatric surgery. A more recent meta-analysis spanning 21 studies with a total of 2374 patients reaffirmed the noted benefit of bariatric surgery in patients with NAFLD with almost 88% of patients achieving improvement in steatosis and 30% having an improvement or resolution in liver fibrosis.

Apart from the long-term sustained weight loss, bariatric surgery also ameliorates NAFLD/MAFLD through multiple other mechanisms including but not limited to enhanced secretion of satiety hormones, variation in dietary habits, improvement in T2DM, alterations in bile acid homeostasis, modification of gut microbiome[116]. Further longitudinal controlled studies are needed to delineate the benefits and type of bariatric surgery as a therapy for those with NAFLD/MAFLD.

Although a few case series on bariatric surgery suggest an acceptable safety profile of these procedures in patients with cirrhosis, a vast majority of these studies included patients with well-compensated cirrhosis. More recently, evolving data demonstrated a modest but nonnegligible risk of complications following bariatric surgery in patients with more advanced cirrhosis. The common complications reported in such patients undergoing bariatric surgery include anastomotic leak, prolonged hospital stay, prolonged intubation, ileus, higher need for blood transfusion, and less commonly sepsis and fulminant hepatic failure[117-120]. As such, bariatric surgery is currently preferred for patients with Child A cirrhosis due to the acceptable risk of complications from surgical and hepatic factors[121-123].

Gut microbiome

Several gut microbiota is known to interact with carbohydrate and lipid metabolism by regulating homeostasis, immunity, and several metabolic pathways. Gut microbiome dysbiosis increases gut permeability thereby increasing exposure of hepatocytes to endotoxins that eventually can lead to hepatocyte inflammation and fibrosis[124]. Studies from animal models suggest that oral administration of prebiotics, probiotics, and synbiotics improves lipid metabolism, dysbiosis, insulin resistance, and hypercholesterolemia associated with hepatic inflammation by altering multiple genes involved in B-oxidation and lipogenesis.

A randomized controlled trial by Vrieze *et al*[125] suggested that FMT improved insulin resistance in Caucasian males with metabolic syndrome thus raising a potential therapeutic option for NAFLD/MAFLD. Needless to say, there is a dire need for more improved and standardized methods of gut microbiome analysis along with a better understanding of interactions between diet, dysbiosis, and environmental factors and their impact on the gut-liver axis to help devise effective and targeted treatment options.

Emerging therapies and future directives

Multiple other studies recently evaluated anti-fibrotic and anti-apoptotic therapies as unique treatment options for patients with NAFLD[126,127]. Albeit the intriguing preliminary results, these studies failed to show considerable clinical benefit in phase 2/3 clinical trials largely due to the limited utility of these drugs in the early stages of NAFLD. The introduction of MAFLD and its diagnostic criteria appear promising as it would potentially allow the incorporation of pharmacotherapeutic agents used in the treatment of metabolic syndrome at an earlier stage in the development of NAFLD.

OUTCOMES

Advanced fibrosis

If left untreated, patients with NAFLD are at risk of advanced fibrosis. A meta-analysis encompassing 11 studies with 411 patients with biopsy-proven NASH showed that 33.6% of patients have eventual fibrosis progression. The annual fibrosis progression rate in patients with NAFLD and stage 0 fibrosis at baseline was 0.07 stages (95%CI, 0.02-0.11 stages), compared with 0.14 stages in patients with NASH (95%CI, 0.07-0.21 stages). These findings correspond to 1 stage of progression over 14.3 years for patients with NAFLD (95%CI, 9.1-50.0 y) and 7.1 years for patients with NASH (95%CI, 4.8-14.3 y)[128]. While baseline demographics such as BMI, age, history of alcohol use, and T2DM play a major role in determining progression to advanced fibrosis, disease-related risk factors such as elevated baseline transaminases, presence of necroinflammation, ballooning degeneration, and Mallory hyaline on

histology are also known to contribute to disease progression[70,129-132].

Advanced fibrosis eventually leads to hepatic decompensation from the development of cirrhosis and end-stage liver disease (2.69 events per 100 person-years). Liver-related mortality is the third cause of death in patients with NAFLD[133].

Hepatocellular carcinoma

Cirrhosis secondary to NAFLD/MAFLD does confer a higher risk of hepatocellular carcinoma (HCC) than those without cirrhosis[134]. Interestingly, the presence of fatty liver disease also confers a higher risk of HCC even in the absence of cirrhosis. Past data suggests that patients with non-cirrhotic NAFLD have a modest risk of HCC when compared to the general population[135,136]. This risk is notably higher in male patients > 65 years with a smoking history, co-existing DM, and/or baseline elevation of ALT[137-144]. As such, performing routine periodic surveillance of these patients with abdominal imaging and measuring alpha-fetoprotein levels could be considered.

CVD

Cardiovascular disease is the most common cause of death among NAFLD/MAFLD patients followed by extrahepatic malignancies[145]. MAFLD is the hepatic manifestation of metabolic syndrome; as such, a vast majority of these patients have additional cardiometabolic risk factors. Indeed, when compared to NAFLD patients a nationwide database study from China demonstrated that MAFLD patients had an increased medium/high 10-year CVD risk according to Framingham risk score [1064 (29.92%) *vs* 1022 (26.37%), $P < 0.005$][146]. While steatosis confers a lesser risk of CVD compared to steatohepatitis, the overall individual risk of CVD ultimately stems from the combination of the stage of fatty liver disease and the presence of other cardiometabolic risk factors. Patients with steatohepatitis and /or advanced fibrosis and those with co-existing T2DM are considered special risk groups for significant cardiovascular events and mortality[147].

In addition to coronary atherosclerosis, NAFLD/MAFLD patients are at a higher risk of cardiac arrhythmias such as atrial fibrillation and ventricular arrhythmias. Furthermore, many NAFLD patients have left ventricular systolic and/or diastolic dysfunction, aortic valve sclerosis, and mitral calcifications [148-153]. While several studies have revealed a higher burden of cardiorenal disease in patients with MAFLD, a recent meta-analysis by Wen *et al*[147] evaluating ten studies suggested a 1.95 times higher incidence of CVD or CVD-related mortality in the MAFLD patients than in the control group[146,154, 155]. Therefore, a thoughtful risk assessment of CVD, evaluation for subclinical atherosclerosis, and presumptive diagnostic studies and interventions for high-risk patients are needed to lower the high global disease burden of CVD in NAFLD/MAFLD patients. Studies evaluating the association of NAFLD/MAFLD, and CVD are listed in Table 1 for further review.

CKD

Chronic kidney disease (CKD) is a worldwide public health problem affecting up to 10%-15% of the general population. More recently, a strong association between NAFLD/MAFLD and CKD has been established independent of commonly co-existing diseases such as obesity, HTN, and T2DM. A meta-analysis by Targher *et al*[156] suggested that NAFLD patients had a considerably higher risk of incident CKD than those without NAFLD. (OR 1.87; 95%CI 1.3-4.1). Few other studies also demonstrated similar findings even after adjustment for potential confounders such as age, sex, BMI, and other well-established metabolic risk factors[157]. Currently postulated etiologies include upregulation of the renin-angiotensin system and impairment of antioxidant defense. Other associated factors that link NAFLD/MAFLD and CKD include metabolic syndrome, platelet activation, dysbiosis, unhealthy eating habits, and aging[158-160].

Since the advent of the new diagnostic criteria for MAFLD, numerous studies have suggested a significant association of MAFLD with CKD, particularly in patients with concomitant DM. A nationwide cohort study evaluating 268946 patients by Jung *et al*[161] revealed a higher adjusted hazard ratio (aHR) for incident CKD in MAFLD patients when compared to those with NAFLD (1.18 (95%CI, 1.01-1.39; $P = 0.040$). Studies evaluating the association of NAFLD/MAFLD, and CKD are listed in Table 2 for further review.

Extrahepatic malignancies

Metabolic syndrome is a well-known risk factor for colorectal cancer. Consequently, several studies have suggested that NASH is independently associated with a heightened risk of colorectal adenomas and advanced colonic neoplasms. Of late, Fukunaga *et al*[162] suggested that MAFLD identifies colorectal adenomas more accurately than NAFLD (OR 3.191; 95%CI 1.494-7.070; $P = 0.003$), with a particularly high risk of colonic adenomas in individuals with non-obese MAFLD (OR 3.351; 95%CI 1.589-7.262; $P \leq 0.001$). Whether NAFLD/MAFLD directly contributes to colon cancer or if colon cancer occurs due to shared metabolic risk factors remains unclear. Patients with NAFLD are believed to have lower adiponectin levels that result in lesser endothelial cell apoptosis and increased proliferation of neoplastic cells, supporting the former possibility of a direct carcinogenic effect of steatohepatitis. Moreover, increased risk of other extrahepatic malignancies such as gastric cancer[163], pancreatic

Table 1 Studies evaluating the risk of cardiovascular disease in patients with nonalcoholic fatty liver disease and metabolic-associated fatty liver disease

Study	Number of patients	Type of study	Outcome measure	Results
Liang *et al* [168]	6873	Cohort Study with a 4.6 yr follow up	Associations of MAFLD and NAFLD with DM, CKD, and CVD	MAFLD was associated with higher risks of CVD (hazard ratio 1.44; 95%CI, 1.15-1.81); Similar associations were observed for NAFLD, except for a higher incidence of DM in MAFLD patients with HBV infection and excess alcohol consumption
Wang *et al* [169]	12183	Cross-sectional study (SPECT – China)	Compare the cardiovascular and renal burden between MAFLD and NAFLD patients	The odds ratio of previous CVD was higher in patients with MAFLD. Male 1.50 (1.22,1.85) *vs* 1.35 (1.1, 1.66); female 1.58 (1.33,1.87) *vs* 1.45 (1.22, 1.72)
Zhang *et al* [170]	19617	Nationwide database study	The burden of CKD and CVD in adults with MAFLD and NAFLD	The cardiorenal burden may be greater for MAFLD than for NAFLD
Lee *et al* [171]	8962813	Cohort study with a 10.1 yr follow up	Association of MAFLD and NAFLD with CVD	MAFLD patients have a higher risk of CKD when compared to NAFLD [1.43 (1.41–1.45) *vs* 1.09 (1.03–1.15)]
Yoneda *et al*[172]	2452949	Nationwide database study	Association of MAFLD and NAFLD with CVD	The incidence rates of CVD were 2.82 (95%CI 2.64-3.01) per 1000 person-yr in the NAFLD groups and 2.69 (95%CI 2.55-2.83) per 1000 person-years in the MAFLD groups
Guerreiro *et al*[173]	1233	Retrospective cross-sectional study	Compare CVR and risk of CVD between patients with NAFLD and MAFLD	In patients with MAFLD and NAFLD, CVR was intermediate/high (36.4 and 25.7%, $P = 0.209$) and CVD occurred in 20.1 and 12.8% ($P = 0.137$) of the cases, respectively, with no influence of liver injury severity
Zhang *et al* [158]	11673	Retrospective study	Compare the risk of CVD between patients with NAFLD and MAFLD	MAFLD was more significant than NAFLD in medium/high 10-yr CVD risk (according to Framingham risk score) [1064 (29.92%) *vs* 1022 (26.37%), $P < 0.005$]
Wen *et al* [147]	-	Meta-analysis	Investigate the risk of CVD incidence or CVD-related mortality in patients diagnosed with MAFLD and NAFLD	The incidence of CVD or CVD mortality was 1.95 times higher in the MAFLD group than in the control group. The risk of CVD or death from CVD was significantly higher in the MAFLD-only group than in the NAFLD-only group, with an RR of 2.57 (95%CI 1.41–4.71; $I^2 = 78\%$, $P = 0.002$)
Guo *et al* [174]	12794	Cohort study	Study the relationship between MAFLD and incident CVD	The incidence of CVD in the patients with MAFLD was significantly higher than that in the non-MAFLD patients (18.38% *vs* 9.02%, $P \leq 0.001$; aHR = 1.37, 95%CI = 1.20-1.56)
Moon *et al* [175]	8919	Cohort study	Effect of MAFLD on future mortality and CVD using a prospective community-based cohort study	T2DM in MAFLD increased the risk of both mortality (HR, 2.07; 95%CI, 1.52 to 2.81) and CVD (HR, 1.42; 95%CI, 1.09 to 1.85)
Zou *et al* [176]	513	Cross-sectional study	Prevalence of MAFLD and its relationship with CVD risks in RA patients	RA patients with MAFLD had a higher rate of CVD events (17.3% *vs* 9.2%) and a higher proportion of high estimated 10-yr CVD risk (55.5% *vs* 26.1%) than those without

MAFLD: Metabolic dysfunction associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease; FL: Fatty liver; FLD: Fatty liver disease; CVD: Cardiovascular disease; CVR: Cardiovascular risk; CKD: Chronic kidney disease; T2DM: Type 2 Diabetes Mellitus; RA: Rheumatoid Arthritis; HR: Hazard ratio; RR: Relative risk; aHR: Adjusted hazard ratio; CI: Confidence Interval; OR: Odds ratio.

cancer[164], esophageal cancer[165], breast cancer[166], and prostate cancer[167] are noted in patients with NAFLD.

Others

Other commonly associated conditions in patients with NAFLD/MAFLD include gastroesophageal reflux disease, obstructive sleep apnea syndrome, psychological dysfunction, hypothyroidism, growth hormone deficiency, and polycystic ovarian syndrome. Despite the substantial research and evidence revealing an association between NAFLD/MAFLD and the aforementioned extrahepatic complications, there are no standardized screening recommendations for these conditions in these patient populations. Careful surveillance and proactive treatment of these extrahepatic complications might improve overall outcomes, morbidity, and mortality in patients with NAFLD/MAFLD.

Table 2 Studies evaluating the risk of chronic kidney disease in patients with non-alcoholic fatty liver disease and Metabolic dysfunction associated fatty liver disease

Study	Number of patients	Type of Study	Outcome measure	Results
Sun *et al*[177]	12571	Cross-sectional study	Association between MAFLD and NALFD with CKD	MAFLD patients had lower GFR (74.96 ± 18.21) and higher prevalence of CKD (29.6%)
Liang *et al* [168]	6873	Cohort Study with a 4.6 yr follow up	Associations of MAFLD and NAFLD with T2DM, CKD, and CVD	MAFLD was associated with a higher risk of CKD (RR 1.64; 95%CI, 1.39-1.94). Similar associations were observed for NAFLD, except for a higher incidence of DM in MAFLD patients with HBV infection and excess alcohol consumption.
Deng *et al* [178]	4869	A cross-sectional study from the NHANES database 2017 – 2018	Association between MAFLD and CKD	Higher prevalence of CKD in MAFLD subjects than in non-MALFD subjects (22.2% *vs* 19.1%, $P = 0.048$)
Wang *et al* [169]	12183	Cross-sectional study (SPECT – China)	Compare the cardiovascular and renal burden between MAFLD and NAFLD patients	OR of CKD was higher in males with NAFLD [CKD: 1.44 (1.05, 1.96) *vs* 1.56 (1.14, 2.12)] than those with MAFLD
Su *et al*[179]	5594	Cross-sectional study	Association between MAFLD and CKD	MAFLD was independently associated with an increased risk of CKD [odds ratio (OR): 1.35, 95%CI: 1.09-1.67]. MAFLD with T2DM had significant associations with increased risk of CKD (OR: 2.85, 95%CI: 2.24-3.63), as well as increased eGFR and UACR
Hu *et al*[180]	15010	Cross-sectional study	Association between MAFLD and CKD	MAFLD was significantly associated with a higher CKD prevalence (OR 1.715, 95%CI 1.389-2.117, $P < 0.001$). MAFLD alone was not an independent risk factor for CKD
Hashimoto *et al*[181]	27371	Cross-sectional study	Association between FLD and MAFLD with CKD	MAFLD was associated with the risk of incident CKD [adjusted hazard ratio 1.24 (1.14-1.36), $P < 0.001$], whereas FLD without MD was not [1.11 (0.85-1.41), $P = 0.433$]
Zhang *et al* [170]	19617	A retrospective nationwide cohort study	Renal burdens in adults with MAFLD and NAFLD	The cardiorenal burden may be greater for MAFLD than for NAFLD
Jung *et al* [161]	268946	A retrospective nationwide cohort study	Association between MAFLD and NALFD with CKD	The adjusted hazard ratio (aHR) for incident CKD in MAFLD was 1.18 (95%CI, 1.01-1.39; $P = 0.040$) compared to those with NAFLD
Tanaka *et al* [182]	13159	Retrospective single-center study	Associations of FL, NAFLD, and MAFLD with the development of CKD	MAFLD [HR (95%CI): 1.12 (1.02-1.26), $P = 0.027$], but not FL or NAFLD, was an independent risk factor for incident CKD

MAFLD: Metabolic dysfunction associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease; FL: Fatty liver; FLD: Fatty liver disease; CVD: Cardiovascular disease; CVR: Cardiovascular risk; CKD: Chronic kidney disease; T2DM: Type 2 diabetes mellitus; HR: Hazard ratio; RR: Relative risk; aHR: Adjusted hazard ratio; CI: Confidence Interval; OR: Odds ratio.

CONCLUSION

The change in nomenclature has impacted the current understanding of fatty liver disease and stimulated more interest from the research community to better understand and treat this silent but deadly condition. As a limitation of our review, it only provides information about what is known and has been published to date as data on MAFLD is emerging. As new evidence becomes available, practitioners will be better able to tackle this disease and prevent its deleterious complications.

FOOTNOTES

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REVIEW

Emerging concepts in the care of patients with cirrhosis and septic shock

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Abstract

Septic shock impacts approximately 6% of hospitalized patients with cirrhosis and is associated with high rates of morbidity and mortality. Although a number of landmark clinical trials have paved the way for incremental improvements in the diagnosis and management of septic shock in the general population, patients with cirrhosis have largely been excluded from these studies and critical knowledge gaps continue to impact the care of these individuals. In this review, we discuss nuances in the care of patients with cirrhosis and septic shock using a pathophysiology-based approach. We illustrate that septic shock may be challenging to diagnose in this population in the context of factors such as chronic hypotension, impaired lactate metabolism, and concomitant hepatic encephalopathy. Furthermore, we demonstrate that the application of routine interventions such as intravenous fluids, vasopressors, antibiotics, and steroids should be carefully considered among those with decompensated cirrhosis in light of hemodynamic, metabolic, hormonal, and immunologic disturbances. We propose that future research should include and characterize patients with cirrhosis in a systematic manner, and clinical practice guidelines may need to be refined accordingly.

Key Words: Cirrhosis; Septic shock; Intravenous fluids; Vasopressors; Antibiotics; Steroids

Core Tip: Septic shock is an important cause of morbidity and mortality among hospitalized patients with cirrhosis. In turn, the pathophysiology of cirrhosis impacts both the diagnosis and management of septic shock in meaningful ways. However, patients with cirrhosis have been traditionally underrepresented in clinical trials for septic shock, leading to critical knowledge gaps. The optimal care of these patients depends on achieving an understanding of the current limitations and implementing strategies for future research to address these shortcomings.

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INTRODUCTION

Among hospitalized patients with cirrhosis, approximately one-third develop sepsis and 6% develop septic shock[1]. Historically, due to unacceptably high mortality rates, individuals with cirrhosis and septic shock were generally considered poor candidates for admission to the intensive care unit (ICU). However, over the past three decades, the findings of randomized controlled trials (RCTs) have led to incremental progress in the management of septic shock, resulting in decreased mortality[2]. Although patients with cirrhosis were underrepresented in these trials, recent epidemiologic studies suggest parallel improvement in survival among this subset, indicating that management in the ICU is warranted[3-6]. While patients with compensated cirrhosis may respond to the same interventions and may have comparable outcomes to those without cirrhosis[7], patients with decompensated cirrhosis and clinically significant portal hypertension have marked local and systemic hemodynamic aberrations and hepatic functional impairment that may profoundly impact their management and prognosis. Consequently, the care of these patients should be appropriately tailored based on their unique pathophysiology. This review highlights the salient aspects of the management of septic shock among patients with cirrhosis and identifies critical knowledge gaps for future research.

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION

Portal hypertension occurs as a result of increased resistance in the hepatic vasculature and nitric oxide (NO)-mediated splanchnic and peripheral arteriolar vasodilation. Together, decreased systemic vascular resistance and increased splanchnic pooling contribute to a state of decreased effective circulating volume. This results in the activation of neurohumoral mechanisms aimed at maintaining adequate tissue perfusion, including beta-adrenergic signaling and the renin-angiotensin-aldosterone system. In patients with portal hypertension, these mechanisms increase cardiac contractility and promote salt and water retention[7]. When a severe infection ensues, macrovascular[8,9] and microvascular[10] vasodilatory effects are exaggerated, further decreasing the effective circulating volume and potentiating the neurohumoral response (Figure 1A).

Irrespective of the etiology of liver disease, 50% of patients develop cirrhotic cardiomyopathy (CCM) as a byproduct of the neurohumoral mechanisms aimed at maintaining the effective circulating volume [11,12]. CCM can manifest with diastolic and/or systolic dysfunction, limiting further augmentation in cardiac contractility in response to hemodynamic stress. Likewise, CCM predisposes to anasarca if excess fluids are administered during resuscitation (Figure 2). Decreased oncotic pressures secondary to hypoalbuminemia and increased hydrostatic pressures secondary to portal hypertension enhance capillary leak.

REPRESENTATION OF CIRRHOSIS IN SEPTIC SHOCK TRIALS

Although individual RCTs investigating diagnostic and therapeutic interventions for the management of septic shock have yielded controversial results, mortality has declined significantly over time. A possible explanation for the lack of benefit observed in trials is the frequent use of overall survival as the primary outcome. This endpoint may be suboptimal in the ICU setting, where the risk of death could be attributed to multiple competing causes[13,14]. In this context, isolated interventions are less likely to influence survival. Heterogeneity in patient selection and disease characteristics and the effects of confounding interventions are additional factors that may impact study results. A neutral association in a RCT may represent benefits for a particular subgroup of patients and harm to another[15]. To

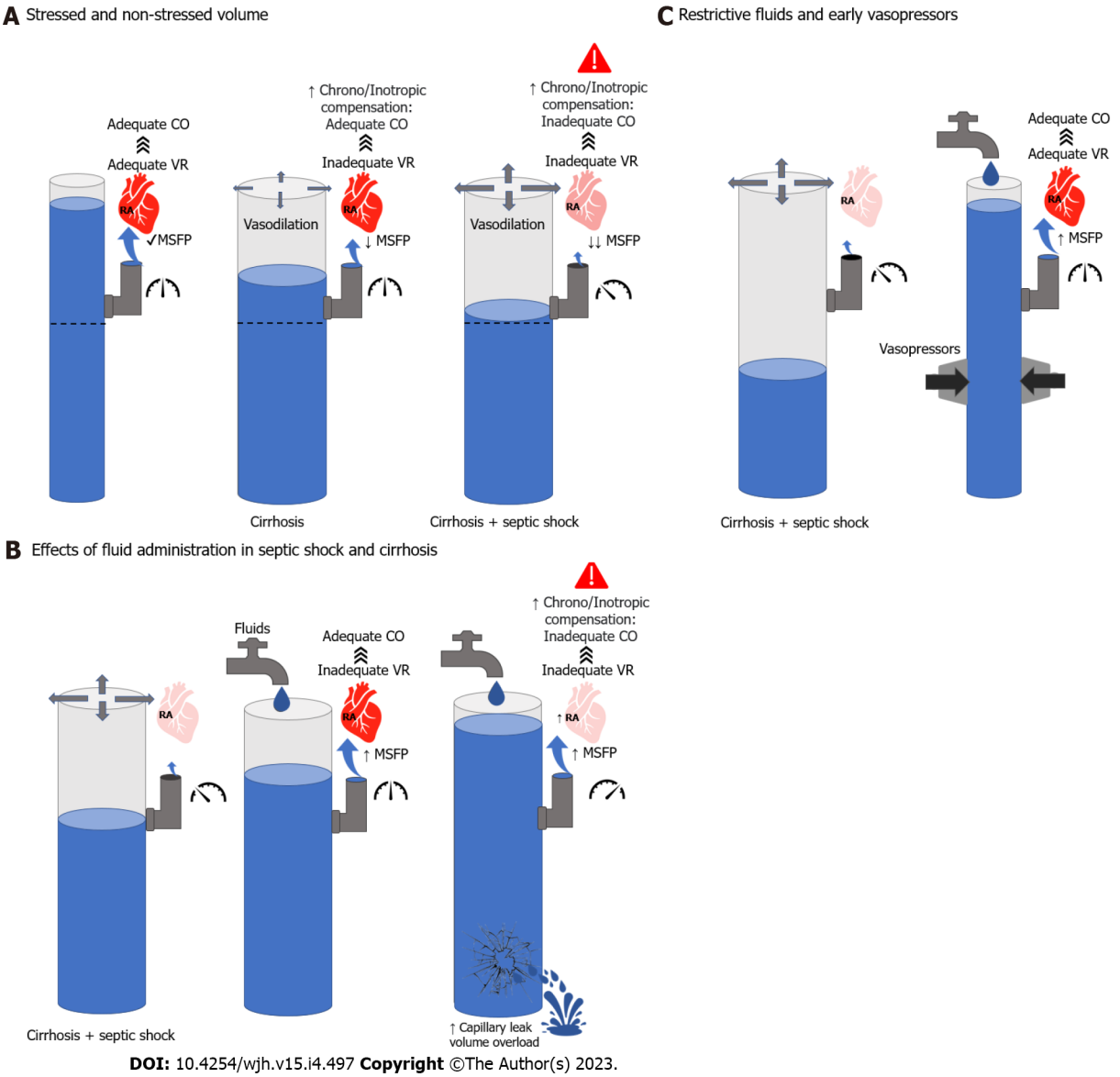

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Figure 1 Hemodynamic considerations in the management of cirrhosis and septic shock. A: *Left*; Normal mean systemic filling pressures (MSFP) leading to adequate venous return and cardiac output (CO). *Middle*; vasodilation in cirrhosis leading to lower MSFP and inadequate venous return (VR). However, compensatory mechanisms are able to maintain adequate CO. *Right*; further vasodilation leading to lower MSFP and inadequate VR. In this case, neurohumoral and cardiac compensation are not enough to maintain CO; B: *Left*; cirrhosis and septic shock pathophysiology. *Middle*; Effects of adequate volume resuscitation leading to increased MSFP. In the context of normal filling pressures, this will increase VR and CO. *Right*; Excessive fluid resuscitation will lead to high filling pressures which will decrease VR and CO. In addition, it may lead to volume overload and capillary leak; C: *Left*; cirrhosis and septic shock pathophysiology. *Right*; adjuvant effect of fluids and vasopressors on MSFP, VR and CO without leading to volume overload. CO: Cardiac output; MSFP: Mean systemic filling pressures; RA: Right atrium; VR: Venous return.

adequately interpret treatment effects among subpopulations such as cirrhosis, large pragmatic trials are required. Unfortunately, most contemporary septic shock trials have either underrepresented, excluded, or mischaracterized patients with cirrhosis (Table 1), limiting the potential applicability of common interventions in this patient population. In some cases, small RCTs of patients with cirrhosis have yielded conflicting results in comparison to those that excluded cirrhosis, leading to controversies in the care of these patients (Figure 3). Throughout the remainder of this review, we will highlight both evidence-based principles and areas of uncertainty.

MANIFESTATIONS OF SHOCK IN CIRRHOSIS

Shock is a state of tissue hypoxia. It occurs when tissue oxygen demands cannot be met by the circulatory system or when tissue oxygen extraction is impaired, leading to cellular dysfunction[16]. It should be considered in patients who develop hypotension with additional clinical or biochemical findings of hypoperfusion, including altered mental status, acute kidney injury (AKI), or lactic acidosis

Table 1 Patients with liver disease in randomized controlled trials of sepsis and septic shock

Trial	Intervention	*n*	Liver disease present (%)	Cirrhosis excluded	Comments
Rivers (2001)	EGDT *vs* Standard	263	61 (23)	No	
ProMISe Trial (2014)	EGDT *vs* Standard	1260	22 (1.8)	No	
ARISE Trial (2014)	EGDT *vs* Standard	1600	83 (5)	No	
ProCESS (2014)	EGDT *vs* Standard	1341	11 (0.8)	No	
ANDROMEDA-SHOCK (2019)	CRT *vs* Lactate clearance	424	0 (0)	Yes	Excluded Child B and C
SMART Study (2018)	Balanced crystalloids *vs* 0.9% NS	15802	180 (11)	No	
BaSICS Trial (2021)	Balanced crystalloids *vs* 0.9% NS and Slow *vs* Fast bolus	11052	266 (2.4)	No	
PLUS Study (2022)	Balanced crystalloids *vs* 0.9% NS	5037	NR	No	
Classic Trial (2022)	Restrictive *vs* Liberal fluids	1554	NR	No	
SAFE Trial (2004)	4% Albumin *vs* 0.9% NS	6997	NR	No	
ALBIOS Study (2014)	20% Albumin + Crystalloids *vs* Crystalloids alone	1818	27 (1.4)	No	Excluded cirrhotic patients with cirrhosis and ascites
VASST Trial (2008)	Vasopressin *vs* NE	778	88 (11)	No	Excluded Na < 130 mEq/L and irreversible disease with less than six-month survival
VANISH Trial (2016)	Vasopressin *vs* NE - AKI	409	14 (4)	No	Factorial design (vasopressin/hydrocortisone)
ATHOS-3 (2018)	Angiotensin-II *vs* Placebo	344	NR	Yes	Excluded MELD > 30
CENSER (2019)	Early NE *vs* Placebo	310	27 (9)	No	
CORTICUS Trial (2008)	Hydrocortisone *vs* Placebo	499	40 (8)	No	
ADRENAL Trial (2018)	Hydrocortisone *vs* Placebo	3800	NR	No	
APROCCHSS Trial (2018)	Hydrocortisone + Fludrocortisone *vs* Placebo	1241	NR	Yes	Excluded Child C

AKI: Acute kidney injury; CRT: Capillary refill time; EGDT: Early goal-directed therapy; NE: Norepinephrine; NR: Not reported; NS: Normal saline.

[17]. Of the various subtypes, septic shock is most common among patients with cirrhosis[18]. It represents a dysregulated immune response to an infection, leading to systemic inflammation, vasodilation, and organ impairment[19].

In patients with cirrhosis and clinically significant portal hypertension, a low mean arterial pressure (MAP) is often present without overt signs and symptoms of hypoperfusion[20]. The ATTIRE trial[21] which included hospitalized patients with decompensated cirrhosis, defined hemodynamic dysfunction as a MAP < 60 mmHg rather than 65 mmHg, illustrating the point that a fixed MAP may not strictly reflect adequate tissue perfusion. Patients with advanced cirrhosis and a chronic state of systemic vasodilation have adaptive autoregulatory mechanisms to maintain perfusion to vital organs despite MAPs < 65 mmHg[22] whereas patients with early cirrhosis, metabolic syndrome, and chronic hypertension may develop tissue hypoperfusion despite MAPs 65 mmHg[23].

Therefore, in addition to assessing blood pressure, a determination of shock relies on assessing perfusion markers. In this respect, it is important to note that the clinical manifestations of hypoperfusion may be less reliable in cirrhosis. For instance, the neurological window for hypoperfusion might represent a diagnostic dilemma in cirrhosis, especially in patients with a history of hepatic encephalopathy (HE). In patients with new or unexplained HE, there should be a high index of suspicion for sepsis or septic shock. Similarly, skin mottling and other skin perfusion signs have lower sensitivity in patients with cirrhosis due to sustained peripheral vasodilation[24].

Another marker of hypoperfusion is type A hyperlactatemia. It occurs when lactate is produced under anaerobic conditions by lactate dehydrogenase[25] and is also confounded in cirrhosis in the context of altered lactate production and clearance. Septic shock is associated with normal to high tissue oxygen delivery but impaired oxygen extraction. Although tissue hypoxia may be present, direct clinical correlation with serum lactate levels may be unreliable in some instances[26-29]. However, peak lactic

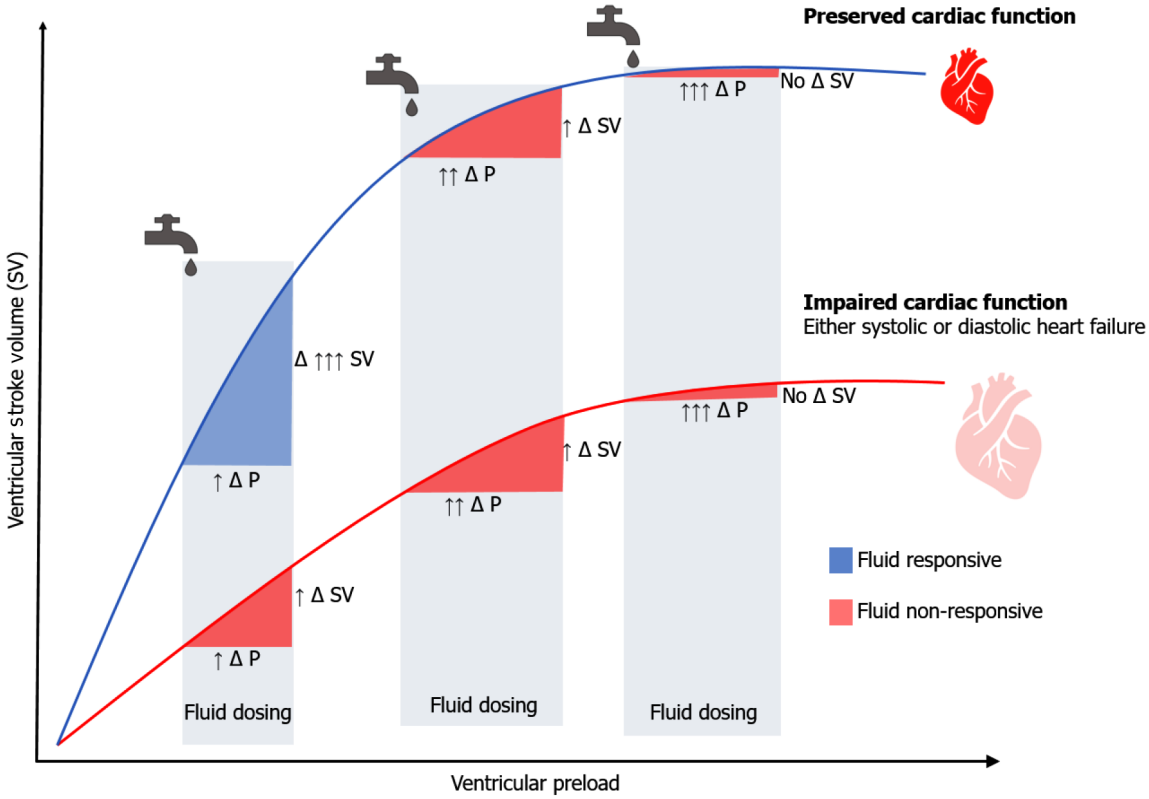

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Figure 2 Frank-Starling curves in septic shock. Every fluid bolus will lead in a change in pressure (Δ P) and a change in stroke volume (Δ SV). The effect of fluids on cardiac output among patients with normal (upper curve) and impaired (lower curve) myocardial function is depicted. Even among patients with normal myocardial reserve, excess fluid administration may significantly increase pressure without significantly increasing stroke volume, which may ultimately lead to anasarca. Δ P: Change in pressure; Δ SV: Change in stroke volume.

acid values and trends have prognostic significance[30]. The contemporary view of hyperlactatemia in septic shock relies on the observation that increased lactate production is driven by beta-adrenergic stimulation, otherwise referred to as stress hyperlactatemia[31]. Stress hyperlactatemia is believed to be a compensatory response to sepsis-induced vasodilation. In a stable hemodynamic state, patients with cirrhosis and more severe liver disease [*i.e.*, those with decompensated disease and/or higher Child-Turcotte-Pugh (CTP) scores] have increased adrenergic tone and higher serum lactic acid values[32]. Because the liver provides up to 70% of the lactate clearance from the body[22], its disproportionate accumulation in patients with cirrhosis and critical illness is not surprising[33,34]. In a propensity score matched analysis accounting for potential confounding factors, Cheng *et al*[35] demonstrated that patients with cirrhosis had higher lactate levels. The difference was particularly robust in those with decompensated cirrhosis (4.08 mmol/L in patients with decompensated cirrhosis who survived *vs* 2.48 mmol/L in patients without cirrhosis who survived and 7.16 mmol/L in patients with decompensated cirrhosis who died *vs* 5.93 mmol/L in patients without cirrhosis who died). Similarly, Drolz *et al*[36] analyzed the predictive value of arterial lactate levels and clearance in critically ill patients with cirrhosis, demonstrating that values greater than 5 mmol/L were independently associated with 28-d mortality, and models such as the model for end-stage liver disease-lactate (MELD-LA) score have incorporated lactate values for prognostication[37]. Higher cutoffs for lactate levels have also been described in critically ill patients with cirrhosis and AKI[38] and in acute liver injury[39]. In the recent Baveno consensus conference, the criteria for futility in patients with variceal hemorrhage included lactate > 12 mmol/L[40]. Finally, it is important to note that, in patients with alcohol use disorder, ethanol oxidation decreases nicotinamide adenine dinucleotide (NAD^+) thereby altering the NAD^+/NADH ratio and shifting pyruvate metabolism toward lactate production. Although its impact on lactate levels appears to be modest[41], clinicians should consider the effects of alcohol use on lactate metabolism[42].

These cumulative data suggest that, although lactate remains useful as a predictor of mortality, the cutoff for normality may be higher in cirrhosis. Venous lactate levels > 2 mmol/L should raise suspicion for shock, but a multimodal approach that accounts for other signs and symptoms of organ hypoperfusion is warranted. In decompensated cirrhosis, a higher threshold (> 4 mmol/L) may be considered [35]. In patients without other signs of hypoperfusion, lactate elevations may indicate progressive physiologic stress and may correlate with poor prognoses but are not necessarily indicative of shock.

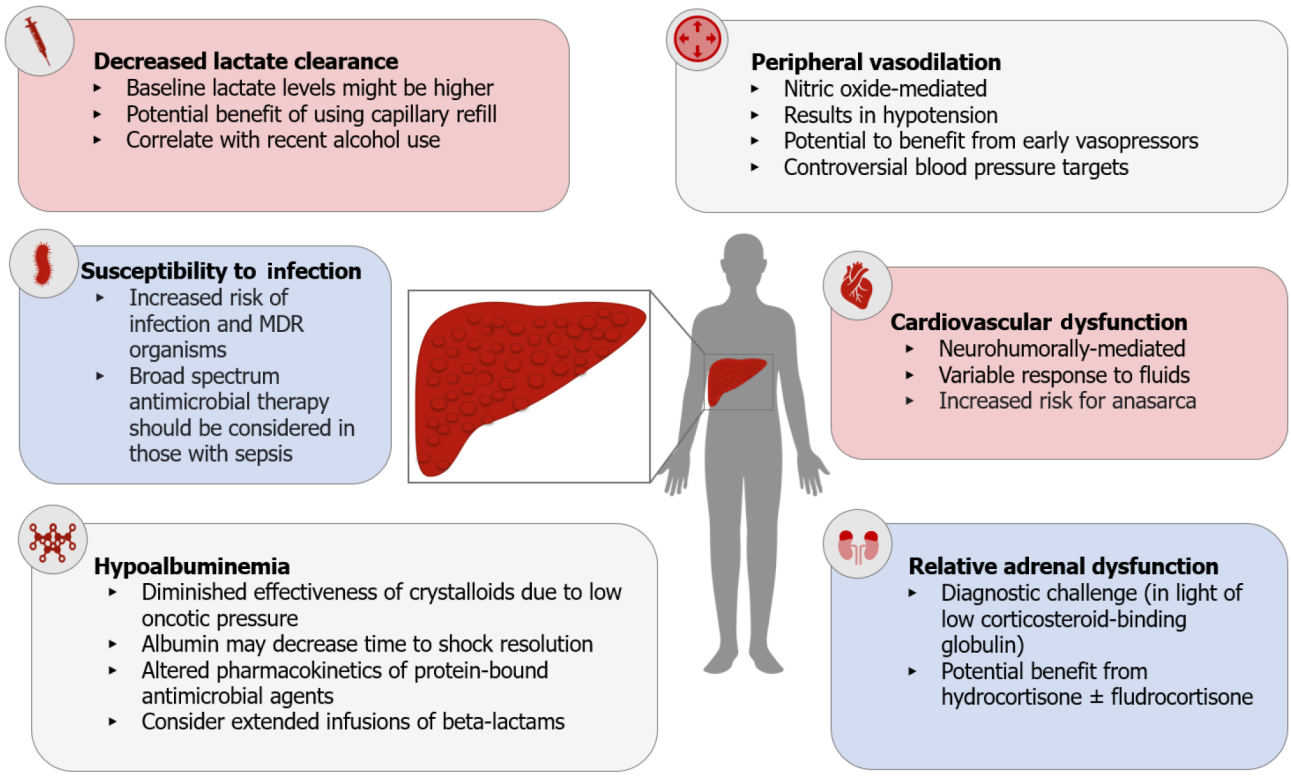

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Figure 3 Pathophysiologic changes in cirrhosis that impact the management of septic shock. MDR: Multi-drug resistant.

This concept has important therapeutic implications.

FLUID RESUSCITATION

The initial management of sepsis is based on a practical evidence-based approach endorsed by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. The Surviving Sepsis Campaign (SSC) guidelines clarify best practices relating to critical aspects of care, including fluid resuscitation, vasopressor, antibiotic use, and steroid use, and hemodynamic monitoring, among other things. In the general population, the timely implementation of some components of this bundle are associated with improved outcomes[43].

Since inception, the SSC continues to suggest the use of at least 30 mL/kg of crystalloids within the first three hours as the initial management of patients with suspected septic shock[44], regardless of initial volume status or degree of volume responsiveness. However, the strength of the recommendation was downgraded from strong to weak in 2021 given the lack of robust data to support aggressive fluid resuscitation[45].

Septic shock is characterized by arteriolar vasodilation and venous pooling, further complicated by hypovolemia due to poor oral intake, insensible losses, and capillary leak in the context of endothelial dysfunction. The rationale for fluid administration is to increase the venous volume and augment the effective circulating volume. If right- and left-sided cardiac filling pressures are not elevated, the use of intravenous fluids may improve cardiac preload. On the dependent (steep) portion of the Frank-Starling curve, increased preload will ultimately augment cardiac output. However, if intravenous fluids are given in the setting of elevated cardiac filling pressures, or if the myocardium lacks inotropic reserve, fluids may not increase cardiac output (Figure 2). On the contrary, venous congestion, interstitial edema, and ineffective gas exchange will ensue (Figure 1B). Critically ill patients who develop anasarca have increased mortality for every liter of positive fluid balance[46,47]. Those with cirrhosis have an even greater risk for complications in light of decreased oncotic pressures and impaired cardiac reserve. Therefore, intravenous fluid therapy should be carefully administered, and as for any other medication, the type, dose, and duration need to be considered.

The type of intravenous fluids used for shock resuscitation are typically classified as crystalloids or colloids. Crystalloids include normal (0.9%) saline or balanced solutions such as Lactated Ringer's, Plasma-Lyte, and Hartmann's solution. Normal saline is the most ubiquitous worldwide, but its use associated with renal dysfunction[48], hyperchloremic metabolic acidosis, and decreased survival[49]. RCTs have demonstrated a potential benefit in favor of balanced crystalloid solutions in comparison to

normal saline in critically ill patients, particularly when large volumes are necessary. Although patients with cirrhosis were underrepresented in these trials[50,51], there is no physiologic rationale against the use of balanced crystalloid in this population. Rather, in light of the risk for kidney injury, the use of hyperchloremic solutions should be limited in patients with cirrhosis.

As a result of the endothelial damage that occurs in sepsis, crystalloids remain in the intravascular compartment for minutes, whereas colloids, such as albumin, remain for up to three hours. In addition, the pleiotropic properties of albumin led to its use in critically ill patients, though RCTs have demonstrated mixed results[52-54]. The ALBIOS trial studied the addition of 20% albumin to crystalloids in hypoalbuminemic patients with severe sepsis or septic shock[54]. Although survival, length of stay, and organ failure scores did not improve, albumin use was associated with higher MAPs, lower net fluid balance, and decreased time to vasopressor or inotrope discontinuation. In a post-hoc analysis of only patients with septic shock, those randomized to the albumin arm had a 6.3% absolute reduction in 90-d mortality (RR 0.87, 95%CI 0.77-0.99; P = 0.03). However, less than 2% of the subjects had liver disease and patients with advanced cirrhosis were excluded from the trial. In the recent FRISC trial[55], investigators compared the use of 5% albumin with 0.9% saline in patients with advanced cirrhosis (mean CTP score of 12 and MELD-sodium score of 33) and sepsis-induced hypotension. The authors found improved hypotension reversal (primary outcome, defined as achieving a MAP ^{3} 65 mmHg at three hours), lower lactate levels, and resolution of tachycardia in the albumin arm. At one week, 43.5% of the patients in the albumin arm were alive in comparison to 38.3% in the normal saline arm (P = 0.03). Similarly, in the recent ALPS study[56] higher rates of short-term septic shock reversal were found using 20% albumin in comparison to Plasma-Lyte. Although albumin use was also associated with more rapid lactate clearance and lower rates of renal replacement therapy, there was no difference in mortality. One in every five patients in the albumin arm required discontinuation of the colloid due to pulmonary edema, most commonly among those with pneumonia. The safety concern of pulmonary edema with the rapid infusion of 20% albumin was also observed in the ATTIRE[21] and CONFIRM[57] studies. Thus, albumin may be effective for shock reversal in patients with cirrhosis, but due to the increased risk for pulmonary complications, close monitoring for volume overload is warranted, specifically in patients with AKI, lung disease, and higher MELD scores.

Finally, the volume of fluid administered also matters. Although no study has directly compared the initial 30 mL/kg of crystalloids to smaller volumes, recent studies have attempted to address the impact of volume. The CLASSIC trial compared restrictive (median 1798 mL) to liberal (median 3811 mL) fluid strategies for resuscitation after an initial administration of one liter of crystalloids[58]. The authors found no differences in 90-d mortality. However, the study provides valuable data regarding the safety of restrictive fluid resuscitation, which could be particularly useful in patients prone to develop volume overload, such as those with cirrhosis. The results of the CLOVERS trial, which tested a similar hypothesis[59] are pending, though the trial was terminated for futility after an interim analysis demonstrated no differences in 90-d survival between both groups. Regardless, it should be noted that weight-based fluid strategies should be reconsidered in some patients, especially those with underlying obesity or marked anasarca. In principle, individualizing fluid resuscitation is an essential principle as requirements and tolerance to fluids vary substantially among individuals[60].

VASOPRESSORS

The application of a restrictive fluid strategy hinges on the early use of vasopressors. Vasopressors target the vasodilatory physiology of septic shock by restoring vascular tone and mobilizing the pooled volume of blood to the heart (Figure 1C). Vasopressors consist of catecholamines such as norepinephrine, epinephrine, dopamine, or phenylephrine and non-catecholamines like vasopressin analogs and angiotensin II. In part, they increase the tone of the vascular bed in patients with septic shock *via* effects on alpha-1 (catecholamines), V1 (vasopressin analogs), or angiotensin II receptors (angiotensin II). The early use of vasopressors leads to a faster resolution of shock[61], whereas delay is associated with increased mortality[62]. In fact, there is an approximately 5.3% increased risk of death for every hour of delay[63]. However, common adverse effects of vasopressors include digital and splanchnic ischemia in a dose-dependent manner[61,62]. Catecholamine-based vasopressors can also lead to cardiac arrhythmias and ischemia due to their effect on beta-1 receptors[64-66].

Based on head-to-head RCTs comparing different adrenergic vasopressors, the SSC recommends norepinephrine as the first line vasopressor for the management of septic shock[45]. Nonetheless, most of these RCTs included less than 10% of patients with liver disease (Table 1). Multiple trials have demonstrated the benefit of vasopressin analogs in hepatorenal syndrome[67-70], a functional manifestation of end-stage portal hypertension characterized by systemic vasodilation and renal vasoconstriction, often precipitated by infections. In this setting, a recent network meta-analysis suggested that terlipressin may be more beneficial than norepinephrine[70]. Terlipressin, is a vasopressin analogue with greater affinity for V1 receptors. It has been proposed as an alternative vasopressor in septic shock. In a small RCT, Choudhury *et al*[71] compared the use of norepinephrine and terlipressin in patients with cirrhosis and septic shock. The authors observed higher rates of shock

resolution, lower incidence of variceal bleeding, and improved time to vasopressor discontinuation with the use of terlipressin. However, a subsequent RCT in patients without cirrhosis showed a higher incidence of adverse events such as digital ischemia when compared to norepinephrine with no improvement in mortality or organ failure resolution[72]. To date, norepinephrine remains the first line vasopressor in patients with septic shock who do not respond to fluids. Although the results of the VASST[73] and VANISH[74] trials did not demonstrate that the early use of vasopressin improved mortality or renal outcomes, respectively, low-dose vasopressin remains the agent of choice after norepinephrine in septic shock because of its relatively favorable side-effect profile and possible pleiotropic effects[75]. Though it may be reasonable to consider vasopressin analogues such as terlipressin in some patients with cirrhosis, there is currently insufficient data to support their use over vasopressin[76-78]. The efficacy of new non-catecholamine based vasopressors such as angiotensin II might be limited in the setting of cirrhosis as hypoalbuminemia was a negative predictor for response in the ATHOS-3 trial[79].

GOALS OF RESUSCITATION

Although the trigger for initiating resuscitation in septic shock is well defined, the endpoint is less clear. The goal of resuscitation is to augment tissue perfusion. However, the resolution of organ dysfunction lags behind the sufficiency of resuscitation, which often leads to excess fluid administration[80]. The ideal targets for adequate resuscitation and the type of monitoring necessary continue to be heavily debated topics.

With the publication of the Rivers study[81], early goal-directed therapy (EGDT) became the cornerstone for the management of septic shock. In this single-center trial, the use of EGDT decreased mortality compared to standard therapy. EGDT consisted of a protocol for the administration of crystalloids, vasopressors, inotropes, and blood products to achieve specific hemodynamic goals (blood pressure, central venous pressure, central venous oxygen saturation, and hemoglobin levels). However, two decades later, three multicenter RCT demonstrated that EGDT does not improve outcomes[82-84] but leads to higher hospitalizations costs[85]. Of note, these trials included a small number of patients with chronic liver disease and cirrhosis (Table 1). Currently, the goals of septic shock resuscitation are to reverse derangements in the very same components that define it. This includes achieving an adequate MAP, improving the signs/symptoms of skin, renal and brain hypoperfusion, and decreasing lactate levels.

First, the SSC guidelines recommend targeting a goal MAP of 65 mmHg over higher values. This recommendation is based on the results of the SEPSISPAM trial which compared high (80-85 mmHg) *vs* low (65-70 mmHg) MAPs. The investigators found no difference in mortality. However, they observed a higher incidence of new-onset atrial fibrillation and lower rates of renal replacement therapy in the high MAP group[23]. The latter was observed only in those with chronic hypertension, suggesting that a personalized target for MAP must be considered, particularly in patients with chronic adaptive mechanisms of autoregulation to higher MAPs.

Of interest, among patients with chronic hypotension, Gershengorn and colleagues demonstrated a robust association between baseline low systolic blood pressure, prolonged use of vasopressors, and increased length of stay[86]. Whether these observations are a consequence of clinicians aiming for unrealistic MAP goals in chronically hypotensive patients or a reflection of more severe disease is unclear. Recently, the results of the 65 trial demonstrated the safety of more liberal MAP goals (60-65 mmHg) in patients with distributive shock[87]. Although these trials did not include patients with cirrhosis, they provide reassurance that lower conventional goals can achieve adequate oxygen delivery and may be adequate targets. Notably, however, as the etiology of cirrhosis has shifted to patients with metabolic syndrome, more patients with chronic arterial hypertension will present with septic shock.

Second, the SSC recommends guiding resuscitation to decrease serum lactate[45]. As mentioned in the previous sections, its use has limitations, particularly in the setting of cirrhosis. However, a decrease in lactate levels after initial resuscitation is associated with improved outcomes, even among patients with cirrhosis[88-91]. In a RCT, Jansen and colleagues tested a lactate-guided strategy for resuscitation based on lactate clearance which led to a significant decrease in mortality. The authors pursued a 20% decrease every two hours for the initial eight hours of management. Interestingly, the levels of lactate within groups were not significantly different, suggesting that perhaps closer monitoring with timely interventions for persistent hypoperfusion rather than lactate clearance is more consequential[91]. Given the caveats of lactate kinetics[92], which are impacted by hepatic clearance[93] and stress-induced production, new alternatives have been proposed.

The ANDROMEDA-SHOCK trial compared the use of capillary refill time (CRT) normalization to lactate clearance in patients with septic shock[94]. The authors demonstrated a non-significant trend towards improved 28-d mortality among the CRT group (HR 0.75, 95%CI 0.55 to 1.02; P = 0.06). Individuals randomized to the CRT arm did receive less fluids and had improvement in organ-dysfunction at 72 h. Zampieri *et al*[95] performed a Bayesian re-analysis of the data, finding a possible mortality benefit with the use of CRT. CRT is now recommended in the SSC guidelines as it offers an

alternative for resuscitation targets, especially in patients in whom lactate clearance is impaired, such as in patients with cirrhosis.

HEMODYNAMIC MONITORING

Whether lactate clearance, CRT, or alternative markers are used as targets for adequate resuscitation, clinicians should assess whether their interventions are achieving the desired effect. Only half of patients with septic shock are volume-responsive during initial resuscitation, around 30% after two hours, and less than 20% after four hours[96]. The hemodynamic response to fluid administration can be assessed by dynamic tests that evaluate whether an increase in preload increases cardiac output[97,98].

Multiple RCTs have demonstrated the feasibility of using fluid responsiveness markers to monitor and guide fluid resuscitation. Their use led to a reduction in the amount of volume administered[99] and need for renal replacement therapy[100], albeit with no effect on survival[101]. Unfortunately, they have not been validated in patients with cirrhosis. Moving forward, the application of tools like point-of-care ultrasonography may help optimize fluid resuscitation in patients with cirrhosis, but studies are necessary to determine the parameters that are most applicable.

ANTIBIOTICS

Early antibiotic administration provides the greatest survival benefit in septic shock. Every hour of delay in their administration conveys an increased risk for mortality[102], even within the first six hours [103]. The SSC guidelines recommend the initiation of antibiotics within one hour of the diagnosis of sepsis with a particular emphasis on patients with shock, for which every hour of delay conveys a 7% increase in mortality[45]. Although the rapid initiation of antimicrobial therapy is essential, the adequacy of coverage and pharmacokinetics are also important in patients with cirrhosis.

Appropriate antibiotic initiation involves administering the drug most likely to eradicate the suspected organism while avoiding unnecessary antibiotic-associated toxicities and exposures that predispose to the development of multi-drug resistant (MDR) organisms[104,105]. In patients with cirrhosis, up to a third of bacterial infections are now due to resistant organisms[106], and these infections are associated with dismal prognoses[107]. Therefore, the choice of empiric treatment, specifically in septic shock, should account for local epidemiology and individual risk factors for MDR infections. Recent hospitalization, nosocomial infection, prior health-care exposure, ICU admission, and recent antibiotics use (within 90 d) predispose to MDR infections in patients with cirrhosis[108,109]. In individuals with these risk factors, broad spectrum antibiotics tailored to local antibiograms and site of infection are warranted, followed by de-escalation within 48-72 h, based on laboratory data and clinical status. Unfortunately, up to 50% of cases of sepsis are associated with insufficient or negative culture data, which complicates both antimicrobial de-escalation and the detection of resistant strains[110]. Rapid diagnostic techniques, which rely on molecular methods such as polymerase chain reaction, are now available for the identification of pathogens and resistance genes. They have been shown to be efficient and effective in isolating the cause of sepsis[111]. Their use is associated with improved antibiotic selection, decreased antimicrobial use[112], shortened hospital stays, and in the case of bloodstream infections, improved mortality[113]. When available, these techniques should be used to optimize the treatment of sepsis. Finally, although the prevalence of fungal infections is variable, patients with cirrhosis have functional defects in neutrophils function that increase the likelihood of infections due to *Candida* and *Aspergillus* species. In general, fungal infections should be strongly considered in patients with abdominal sepsis, exposure to broad spectrum antibiotics or steroids, parenteral nutrition, prolonged ICU stay[114], and ACLF[115].

In cirrhosis, altered pharmacokinetics and pharmacodynamics modify the efficacy of antimicrobial agents. For highly protein-bound antibiotics such as ceftriaxone, aztreonam, or carbapenems, hypoalbuminemia increases the unbound fraction and increases its clearance[116], resulting in lower drug levels over the minimal inhibitory concentration (MIC). For antibiotics such as beta-lactams, for which efficacy depends on the time over the MIC, this may lead to treatment failure[117]. In patients with hypoalbuminemia the use of ertapenem is associated with a fivefold increase in mortality, which is not observed with lower protein-bound carbapenems such as meropenem or imipenem[118]. Furthermore, patients with ascites have an increased volume of distribution, which may result in decreased peak concentrations of antibiotics, especially those which distribute extracellularly[119]. In the case of spontaneous bacterial peritonitis, a common source of sepsis among hospitalized patients with cirrhosis, peritoneal antibiotic penetration is an essential concept. While some agents like cephalosporins, fluoroquinolones, and meropenem[120-122] achieve high concentrations in ascitic fluid, others such as aminoglycosides and tigecycline have reduced penetration[123,124]. The use of continuous or extended infusions of beta-lactams increases the duration of antibiotic levels over the MIC and lead to higher cure rates and decreased mortality in RCTs among patients without cirrhosis[125-127]. In a secondary analysis of the BICHROME study, Bartoletti *et al*[128] compared extended infusions *vs* bolus dosing of carbapenems or

piperacillin/tazobactam in patients with cirrhosis who had bloodstream infections. The authors found that extended infusions were associated with improved mortality and higher rates of hospital discharge. Currently, the use of prolonged infusions of beta-lactams is recommended in patients with sepsis and septic shock[45].

ADRENAL DYSFUNCTION

Corticosteroids provide anti-inflammatory counterbalance to the dysregulated inflammatory response. They counteract vasodilatation by acting on endothelial glucocorticoid receptors[129], potentiate catecholamine effects, and contribute to volume retention. Therefore, hydrocortisone is recommended for the treatment of septic shock refractory to norepinephrine (at doses > 0.25 mg/kg/min)[45], although multiple RCTs have yielded conflicting data about their efficacy[130-134]. In 2018 the results of the most recent trials ADRENAL[135] and APROCCHSS[136] were published. In the former, the investigators tested the administration of continuous intravenous hydrocortisone against placebo for seven days in patients with septic shock. Although the authors did not observe a mortality benefit, time to shock reversal, length of ICU stay, and mechanical ventilation duration were all reduced in the hydrocortisone group[137]. In the APROCCHSS trial, investigators compared bolus intravenous hydrocortisone plus oral fludrocortisone to placebo, demonstrating improved survival and faster shock resolution[136]. Based on these mixed results, Pirracchio *et al*[138] used data from these RCTs in a machine learning model to explore the individual treatment effect of corticosteroids based on individual estimates of benefit. The authors found that corticosteroid administration based on risk modeling yielded benefit compared to a treat-all-or-none approach. However, the impact of the presence or absence of cirrhosis was not assessed.

The number of patients with cirrhosis in studies evaluating the role of steroids in septic shock is low (Table 1). Nonetheless, 50%-80%[139-141] of patients with advanced cirrhosis have normal baseline cortisol secretion but impaired response to stress; a state called relative adrenal insufficiency (RAI). In stable patients with cirrhosis, RAI is diagnosed and managed according to the adrenal response to ACTH stimulation[142], but in critically ill patients, its use to characterize and manage RAI is discouraged[143].

The high prevalence of RAI would suggest a clear benefit in favor of corticosteroids among patients with cirrhosis, but the evidence for their efficacy is mixed. In a prospective observational study, Ferná ndez *et al*[144] demonstrated that corticosteroids conferred improved survival and faster shock resolution. In a small RCT, Arabi *et al*[145] noted improvements in shock resolution but no survival benefit. Patients treated in the corticosteroid arm had a higher incidence of shock relapse, which supports the notion of unmasked RAI. A higher incidence of gastrointestinal bleeding was observed in the Arabi trial, but this was not replicated in larger observational studies[146]. Despite the mixed evidence, SSC guidelines currently recommend the use of corticosteroids in patients with refractory shock[45].

CONCLUSION

The management of patients with cirrhosis and septic shock is largely based on data extrapolated from RCTs of patients without cirrhosis. However, in light of key differences in pathophysiology, basic interventions may be associated with different outcomes in this subset. Although the SSC guidelines have streamlined and improved the management of septic shock in the general population, these recommendations must ultimately be individualized for patients with cirrhosis using evidence-based strategies. In light of the growing impact of cirrhosis on the care of critically ill patients, future research in septic shock should focus on including and accurately characterizing this population in an effort to overcome critical knowledge gaps.

FOOTNOTES

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MINIREVIEWS

Ablative strategies for recurrent hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is the fifth leading cause of cancer death worldwide and the third leading cause of all diseases worldwide. Liver transplantation, surgical resection and ablation are the three main curative treatments for HCC. Liver transplantation is the optimal treatment option for HCC, but its usage is limited by the shortage of liver sources. Surgical resection is considered the first choice for early-stage HCC, but it does not apply to patients with poor liver function. Therefore, more and more doctors choose ablation for HCC. However, intrahepatic recurrence occurs in up to 70% patients within 5 years after initial treatment. For patients with oligo recurrence after primary treatment, repeated resection and local ablation are both alternative. Only 20% patients with recurrent HCC (rHCC) indicate repeated surgical resection because of limitations in liver function, tumor location and intraperitoneal adhesions. Local ablation has become an option for the waiting period when liver transplantation is unavailable. For patients with intrahepatic recurrence after liver transplantation, local ablation can reduce the tumor burden and prepare them for liver transplantation. This review systematically describes the various ablation treatments for rHCC, including radiofrequency ablation, microwave ablation, laser ablation, high-intensity focused ultrasound ablation, cryablation, irreversible electroporation, percutaneous ethanol injection, and the combination of ablation and other treatment modalities.

Key Words: Hepatocellular carcinoma; Recurrence; Ablative therapy; Thermal ablation

Core Tip: Despite the tremendous efforts in the fight against hepatocellular carcinoma, there is still no way to prevent its recurrence. Intrahepatic recurrence can be treated by repeated resection and ablation, and there are many studies showing the advantages and disadvantages of each treatment method. For tumors ≤ 3 cm in diameter, there is no significant difference between surgery resection and radiofrequency/microwave ablation treatment. Non-thermal ablation treatment has clearer borders but a higher postoperative recurrence rate. Percutaneous ethanol injection has comparable efficacy to radiofrequency ablation for small tumors. Multiple recurrences require combined systemic therapy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third leading cause of cancer death worldwide[1]. Up to 20% of HCC patients relapse within 2 years after liver transplantation and 1/3 of post liver transplantation patients with recurrent HCC (rHCC) experienced late recurrence (> 5 years after liver transplantation)[2]. Nearly half of patients with early-stage HCC experienced recurrence after Hepatic resection[3]. The local recurrence rate in patients with HCC treated radiofrequency ablation (RFA) varied between 18.2% and 46.6%[4].The incidence of intrahepatic and extrahepatic recurrence had been reported to be approximately 70% eventually[5,6]. Thus, the treatment and management of HCC recurrence is very important.

rHCC can be divided into two types: Oligo recurrence and disseminated recurrence[7,8]. Patients with oligo recurrence were consider for radical treatment, including surgery and RFA[9]. Whereas patients with disseminated recurrence received palliative treatment or supportive care only[9]. The curative approaches for intrahepatic rHCC include salvage liver transplantation, repeat resection and RFA. Salvage liver transplantation has been proposed to be the optimal option but have precluded its extensive application because of the shortage of organ donors and the strict selection criteria for patients [10-12]. In addition, because of progressive liver dysfunction, the presence of multiple tumors, various tumor sites, and intraperitoneal adhesions, only 20% patients with recurrence are eligible for repeated resection[13,14].

Ablation has the advantages of minimal invasiveness, fewer complications and good repeatability [15]. Ablative therapy is a locoregional treatment that can be used alone or in combination with other treatment modalities[16]. Monotherapy includes RFA, microwave ablation (MWA), laser ablation (LA), high-intensity focused ultrasound (HIFU) ablation, cryoablation (CRA), irreversible electroporation (IRE), and percutaneous ethanol injection (PEI). Combination therapy includes RFA/MWA-transcatheter arterial chemoembolization (TACE) and RFA-PEI.

RADIOFREQUENCY ABLATION

RFA generates 400-500 kHz radiofrequency current through the distal end of the uninsulated part of the puncture needle, which causes high-frequency friction of water molecules in the tumor tissue and local high temperature, leading to co-degeneration necrosis and protein degeneration in the tumor tissue[4, 17,18]. RFA is one of the curative treatment modalities for early-stage HCC with advantages of safety, tolerability, ease of operation, and cost-effectiveness[4]. Previous study has demonstrated that RFA provided similar long-term survival rates for isolated HCC of 5 cm or less, regardless of whether the treatment was initial or salvage therapy[19]. Indications of RFA for rHCC are the same as those for initial HCC, including single nodule < 5 cm in diameter or less than 3 nodules with the largest diameter < 3 cm, and without vascular invasion nor extrahepatic metastasis[15].

There were no significant differences in overall survival (OS), re-recurrence rate, distant progression-free survival rate, local progression-free survival rate, nor complications between RFA and repeated resection in early-staged rHCC[16,20]. Another recent randomized controlled trial showed no statistically significant difference in OS and repeat recurrence–free survival (RFS) between repeated resection and RFA in early-staged rHCC[21]. Additionally, in patients with rHCC diameter greater than 3 cm or alpha-fetoprotein level greater than 200 ng/mL, local disease control and long-term survival may be better with repeated resection[21]. Moreover, thermal ablation is superior to repeated resection in safety, such as significantly shorter average hospital stay, less risk of intraoperative blood transfusion, and less invasive[16,22,23].

The main contraindications of RFA are severe bleeding diathesis (platelet count less than 50000/μL), hemostatic compromise, decompensated ascites, jaundice and the presence of metallic devices such as pacemakers[24]. Relative contraindications are lesions near the gastrointestinal tract, biliary system and heart. RFA should also be avoided for tumors within 1 cm proximal to the hepatic portal tract[24].

MICROWAVE ABLATION

MWA causes cell death by increasing the temperature of tumor tissue caused by electromagnetic energy deposition in the tumor[25]. The advantages of MWA over RFA are as follows: (1) MWA uses electromagnetic wave energy without grounding poles, so it does not cause skin burns and has no taboos to metals[26]; (2) The electromagnetic field of the MWA causes rapid and uniform heating of the tissue, creating a more uniform and predictable ablation zone with less time; and (3) MWA provides faster heating and higher temperature, so MWA is suitable for perivascular, subcapsular lesions and those adjacent to bile duct[27-29]. Previous study has demonstrated no significant difference in OS nor disease-free survival (DFS) between MWA and surgical resection[30]. Meanwhile, the meta-analysis demonstrated that MWA was associated with shorter operation time, less amount of blood loss in operation, and less complications when compared to surgical resection[30].

The complications of MWA and RFA are similar, such as bleeding, liver abscess, hemothorax, colon perforation and bile duct stenosis[31].

LASER ABLATION

LA is a procedure based on laser devices that convert heat energy into light energy and generate heat with tissues to cause cell death[32] and was firstly described in 1983 for the treatment of liver tumors [33].

A randomized controlled trial confirmed LA should be considered a viable treatment option for HCC ≤ 20 mm, given lower incidence of complications than the RFA group and comparable primary technique efficacy rate and RFS rate[34]. Traditional thermal ablation techniques (RFA and MWA) are considered less effective than TACE in obtaining a complete response for solitary large HCC ≥ 40 mm [35-37]. A recently published retrospective case-control study indicated that multifiber LA approach was more effective than TACE by achieving a complete tumor ablation and reducing the recurrence rates[38]. However, LA is rarely used and has been superseded by MWA or RFA in many centers partly because LA requires a high level of equipment and its results need to be confirmed by randomized controlled trials[39].

HIGH-INTENSITY FOCUSED ULTRASOUND ABLATION

HIFU ablation is a non-invasive ablation mode using an ultrasound frequency of 0.8-3.5 MHz focused through intact skin on a distant therapeutic transducer[40,41]. Compared with RFA, HIFU has the following advantages: (1) HIFU is an *ex vivo* conformal therapy without invasiveness; (2) Tumor seeding is unlikely to occur in HIFU; and (3) No direct puncture of target tumor[42].

HIFU is currently used mainly for palliative treatment of advanced HCC[43]. There was only one retrospective study showed that the OS of HIFU was slightly higher than that of RFA, but the DFS was lower than that of RFA, and the procedure-related morbidity was lower after a median follow-up time of 27.9 mo of patients with rHCC[44]. Notably, this study was retrospective in nature and had a small sample size.

The main limitation to the clinical application of HIFU is the long ablation time required. Other challenges are the difficulty in precise localization and monitoring, and the difficulty in transmitting ultrasonic energy through the covering bone structure to the lesions behind the ribs[45]. The main systemic changes of HIFU are fever, supraventricular tachycardia, hypertension. The local complications are skin burns, pain, mild impairment of hepatic function and mild hematuria[46].

CRYOABLATION

CRA uses extremely low temperatures to directly cause intracellular and extracellular ice crystal formation and lytic agent deformation, leading to cell dehydration and rupture. Vascular injury leads to ischemic hypoxia indirectly destroying tumor tissue. CRA has several potential advantages over RFA: (1) Multiple probes can be used simultaneously to produce a large puck; (2) the size and shape of the puck produced by cryotherapy can be easily seen by intraoperative computed tomography (CT), magnetic resonance imaging, or ultrasound; and (3) relatively painless procedure compared to thermal-

based ablation, which can be performed under local anesthesia rather than the general anesthesia required for radiofrequency ablation[47].

The efficacy of CRA for HCC has been demonstrated by a large study cohort including 1595 patients with 2313 tumors[47]. The complete response (CR) rates were 81.2% (1893/2313), 99.4% (780/784), 94.4% (1622/1719), and 45.6% (271/594) in all tumors, tumors < 3 cm, tumors < 5 cm, and tumors > 5 cm, respectively. The CR rate was high than that for RFA that ranged from 50% to 80% in HCCs of 3 to 5cm[48]. At present, the application of CRA in the treatment of rHCC has not been reported.

The most common complications of CRA are postoperative pain, postoperative fever, transient elevations of alanine aminotransferase, hepatic hemorrhage, liver and pleural abscesses and cryoreaction (chills, fever, tachycardia, tachypnea and temporary renal damage, *etc.*)[49,50]. CRA is recommended as first-line therapy for tumors < 5 cm. For tumors > 5 cm, CRA can reduce tumor burden [47].

IRREVERSIBLE ELECTROPORATION

IRE works by generating high voltage (> 640 V/cm) and high intensity (> 20 A) electrical pulses of short duration (70–100 μs) which render the cellular bilipid membrane of the cells permanently irreversible porous[51,52]. IRE is a good option for patients who cannot undergo surgery, thermal ablation surgery, or whose tumors are close to important structures[51].

A recent meta-analysis reported an OS of 81.3% at 12 mo, 61.5% at 2 years, and 40.9% at 3 years; PFS was reported as 64.2% at 12 mo and 49.1% at 2 years[53]. Since RFA and MWA are preferred in tumors located at "non-risk" locations and IRE is used in "high location", the efficacy of IRE cannot be directly compared with RFA and MWA in a clinical setting[53].

The major complications are liver abscess, hemorrhage, fever, mild pleural effusion, mild hemoperitoneum, subcapsular hematomas, atrial fibrillation and partial portal vein thrombosis[54-57].

PERCUTANEOUS ETHANOL INJECTION

Injection of ethanol caused dehydration and necrosis of tumor cells accompanied by thrombosis in small vessels to kill tumor tissue[58]. A matched case-control comparative analysis showed that the OS of PEI is comparable to RFA in patients with HCC smaller than 1.5 cm[59]. The major limitation of PEI is significantly higher local recurrence than RFA[60,61]. Interestingly, recent studies have shown that the combination of PEI with RFA in the treatment of HCCs provides comparable OS rates and RFS.

The mechanisms of RFA-PEI are as follows: (1) RFA enhances the ablative effect of ethanol due to its low boiling point (78.3 °C); (2) Ethanol embolizes small vessels to reduce the heat-sink effect; (3) Ethanol distributes to RFA enabled areas (or difficult-to-treat areas); (4) Ethanol diffuses beyond the RFA ablation zone to establish a safety margin; and (5) An ethanol makes the tissue around the electrode less prone to carbonization and further thermal conduction[62-64].

A retrospective study enrolled 271 patients to compare combined RFA-PEI with hepatic resection in the treatment of resectable solitary HCC with 2.1-5.0 cm diameter[65]. RFA-PEI had higher OS rates at 1, 3, and 5 years and RFS rates at 1, 3, and 5 years over hepatic resection in the treatment of solitary HCCs, especially for those with 2.1-3.0 cm in diameter. Additionally, RFA-PEI was superior to hepatic resection in major complication rates, length of hospital stay and cost. A meta-analysis showed that for tumors with 3-5 cm in diameter, the 2-year OS was slightly higher in the RFA-PEI than in the RFA group[66]. There were another two studies showed significant clinical improvements in the combination group in terms of the 1-/1.5-/2-/3-/5-year OS[67,68]. Furthermore, post-procedural major complications and pain did not significantly differ between the RFA-PEI groups and RFA groups[69]. A retrospective study found that the combined RFA-PEI group had comparable OS and RFS to repeat hepatectomy for elderly patients with small rHCC after hepatectomy, but with shorter hospital stays and lower rates of major complications and non-tumour-related deaths[70]. In summary, combined therapy with RFA-PEI is suitable for 2 to 3 cm lesions with liver function compensation.

ABLATION COMBINED WITH TACE

Iodized oil and gelatin sponge particles used in TACE can increase RFA- or MWA-induced coagulation necrosis by going through multiple arterio-portal communications. TACE enhances heat transfer in RFA or MWA treatment by blocking hepatic arterial blood flow and reducing perfusion-mediated hepatic blood flow cooling (heat-sink effect)[4,24]. It has been improved in: (1) Minimizing heat loss due to the heat-sink effect; (2) increasing the area of coagulative necrosis; (3) producing more thorough necrosis within the mass; and (4) enlarging the ablation margin, destroying the satellite lesion[4,24,71]. In addition, the digital subtraction angiography technique during TACE helps to detect multiple small

tumors and subsequent eradication these tumors[72].

A recent study by Li *et al*[73] that included 3000 cases of HCC showed the OS rate and CR rate of the TACE-RFA group was significantly higher than the TACE alone group[73]. Another review presented that TACE-RFA combined therapy and surgical resection had a similar 1-year OS rate, 3-year OS rate, 1-year RFS rate, and 3-year RFS rate for early HCC[74]. However, the 5-year OS rate and 5-year RFS rate were lower in patients with TACE-RFA than in those with surgical resection. Furthermore, there were two studies found that TACE-RFA treatment is superior to RFA used alone in OS and RFS[75,76]. A recent study demonstrated that for HCC patients with microvascular invasion (MVI) and rHCC up to three nodules smaller than 3 cm within 2 years, TACE-RFA could achieve better secondary RFS than repeated resection or RFA alone, while RFA alone had survival benefits comparable to repeated resection in other rHCC patients with small recurrence[77]. There was a study that selected 186 patients who underwent TACE-RFA (n = 107) or repeated resection (n = 79) for rHCC with a diameter < 5 cm [72]. It showed fewer complications and shorter hospital stays in the TACE-RFA group than in the repeated resection group, and there were no significant differences in OS nor RFS.

A recent study conducted by Zaitoun *et al*[78] screened 278 patients with HCC 3-5 cm, and patients were randomized into three groups: 90 underwent TACE (group 1); 95 underwent MWA (group 2); and 93 underwent combined therapy (group 3)[78]. Their study found that group 3 had the significantly lower recurrence rate after 12 mo, and the significantly higher OS and mean progression-free survival than groups 1 and 2. Therefore, the combination of thermal ablation with TACE therapy is an optimal choice for patients with HCC tumors > 3 cm[78,79].

RFA or MWA can be performed the same day or less than 2 wk after TACE[75,78]. The most common complications of TACE-RFA are gastrointestinal bleeding, abscess, liver failure, liver infarction[71].

PERCUTANEOUS VS LAPAROSCOPIC TECHNIQUES

Thermal ablation can be performed safely using percutaneous or laparoscopic techniques. RFA was generally applied to HCC patients who could not endure repeated resection of the tumor or were not eligible for liver transplantation. RFA is commonly used to eliminate percutaneous tumors and is the most appropriate method for HCC masses far from the intestine, bile duct, ureter, or diaphragm[80]. In contrast, the laparoscopic RFA (LRFA) procedure requires general anesthesia, so the patient is more cooperative, the ablation boundaries are clearer, and the ablation can reach deeper. Therefore, laparoscopic RFA performed better than PRFA in the deep-seated liver cancers, such as subphrenic lesions[81].

According to Kwak *et al's* study[82] on subphrenic HCC, the local tumor progression rate of the LRFA group was significantly lower than that of the PRFA group, the cumulative OS rate of the LRFA group was significantly higher than that of the PRFA group, and there was no statistical difference in DFS rate between the two groups[82]. Another study showed that laparoscopic MWA seemed to have a tendency to be more effective than percutaneous MWA in the treatment of subcapsular HCC[83]. However, the laparoscopic approach has a higher rate of postoperative complications than the percutaneous approach [80,82,83]. Consequently, LRFA can be a valuable treatment option for subphrenic and subcapsular HCC if accessible using the laparoscopic approach.

ABLATION VS OTHER LAGICAL TREATMENT

Apart from ablation, non-operative local treatment of HCC includes TACE, stereotactic body radiation therapy (SBRT) and Proton beam radiotherapy (PBT). Many articles have shown that RFA has long-term benefits comparable to repeat hepatectomy (RH) for tumours less than 3 cm[16,20,21,84]. The study showed that RFA has better OS and RFS advantages than TACE for rHCCs in both ≤ 3 cm and > 3 cm lesions[84]. RFA and SBRT showed considerable therapeutic benefit for rHCC ≤ 3 cm, better OS but lower RFS rate for rHCC > 3 cm[84]. A prospective randomized study showed that the LPFS rate of PBT was comparable to that of RFA observed in rHCC patients with ≤ 2 tumor (s) of < 3 cm[85].

The 2-year OS was slightly higher in the RFA-PEI than in the RFA group, and current evidence was difficult to draw a definite conclusion regarding the therapeutic management in terms of local recurrence free proportion and complete tumor necrosis. However, TACE-RFA is comparable to RH in both OS and RFS, and has a lower complication rate and hospital stay than RH. Therefore, in patients with liver function compensation, TACE-RFA local therapy may be considered as a preferred option.

The use of percutaneous fusion imaging-guided RFA is effective and safe for the treatment of subcentimeter rHCC[86]. However, PRFA was not feasible in 34.3% (72/210) of sub-centimeter rHCCs primarily due to poor lesion conspicuity[87]. And fusion imaging with or without CEUS does not always satisfactorily locate sub-centimeter rHCC. Cone-beam CT-guided TACE can also be used as an alternative local therapy for subcentimeter rHCC due to its high technical feasibility and detectability [88].

Table 1 Application of various minimally invasive treatments in hepatocellular carcinoma

Tumour size	Patients condition	Treatment
Sub-centimeter	Percutaneous tumors	PRFA
	Local ablation therapy is not feasible	TACE
< 3 cm	Percutaneous tumors	PRFA
	Subphrenic and subcapsular tumors	LRFA
	Perivascular tumors	MWA
	Can't endure thermal ablation	CRA
	MVI (+)	TACE-RFA
3-5 cm	With liver function compensation	TACE-RFA
	Liver failure	MWA, CRA

PRFA: Percutaneous radiofrequency ablation; LRFA: Laparoscopic radiofrequency ablation; TACE: Transarterial chemoembolization; MWA: Microwave ablation; CRA: Cryoablation; MVI: Microvascular invasion.

CONCLUSION

This review methodically describes the treatment of rHCC by various ablation procedures in recent years. Moreover, this study compares the indications, advantages and survival analysis of various ablative treatments. Therefore, we summarize how to choose the appropriate ablation therapy for different rHCC patients (Table 1).

RFA, MWA and CRA can be considered recommended as first-line treatment for rHCC < 3 cm in diameter. RFA is currently the most widely used, PRFA can be used in percutaneous tumors and LRFA can be used in subphrenic and subcapsular tumors, while MWA is more recommended for patients with perivascular lesions and TACE-RFA could be consider for patients with MVI (+). CRA is an option for patients who are not candidates for thermal ablation. For patients with 2 to 3 cm lesions with liver function compensation, PEI-RFA can be selected. TACE combined with RFA/MWA provided better overall and disease-free survival than TACE alone. For tumors with diameter ranging from 3 to 5 cm, MWA, CRA, and TACE-RFA are recommended. Remarkably, TACE-RFA is a better choice for patients with 3-5 cm rHCC with liver function compensation. For tumors > 5 cm in diameter, local ablation can reduce the tumor burden as a bridging therapy during the waiting period for liver transplantation, or as palliative treatment for recurrence after liver transplantation. In conclusion, the treatment decisions were individualized requires a professional liver surgeon to consider the patient performance status, liver function, and recurrent tumor status.

FOOTNOTES

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MINIREVIEWS

Therapeutic possibilities of gut microbiota modulation in acute decompensation of liver cirrhosis

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Abstract

The formation of liver cirrhosis (LC) is an unfavorable event in the natural history of chronic liver diseases and with the development of portal hypertension and/or impaired liver function can cause a fatal outcome. Decompensation of LC is considered the most important stratification variable for the risk of death. It is currently postulated that decompensation of LC occurs through an acute (including acute-on-chronic liver failure) and non-acute pathway. Acute decompensation of LC is accompanied by the development of life-threatening complications, characterized by an unfavorable prognosis and high mortality. Progress in understanding the underlying molecular mechanisms has led to the search for new interventions, drugs, and biological substances that can affect key links in the pathogenesis of acute decompensation in LC, for example the impaired gut-liver axis and associated systemic inflammation. Given that particular alterations in the composition and function of gut microbiota play a crucial role here, the study of the therapeutic possibilities of its modulation has emerged as one of the top concerns in modern hepatology. This review summarized the investigations that describe the theoretical foundations and therapeutic potential of gut microbiota modulation in acute decompensation of LC. Despite the encouraging preliminary data, the majority of the suggested strategies have only been tested in animal models or in preliminary clinical trials; additional multicenter randomized controlled trials must demonstrate their efficacy in larger patient populations.

Key Words: Liver cirrhosis; Acute decompensation; Pathogenesis; Therapy; Gut microbiota; Modulation

Core Tip: Given that particular alterations in the composition and function of gut microbiota play a crucial role in the pathogenesis of acute decompensation in liver cirrhosis (LC), this review summarized the investigations that describe the theoretical foundations and therapeutic potential of gut microbiota modulation in acute decompensation of LC. Despite the encouraging preliminary data, the majority of the suggested strategies have only been tested in animal models or in preliminary clinical trials. Additional multicenter randomized controlled trials must demonstrate their efficacy in larger patient populations.

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INTRODUCTION

The formation of liver cirrhosis (LC) is an unfavorable event in the natural history of chronic liver diseases and with the development of portal hypertension and/or impaired liver function can cause a fatal outcome. During LC, there is a compensated stage, which is usually asymptomatic and characterized by preserved quality of life and a median survival exceeding 12 years, and a decompensated stage associated with the occurrence of life-threatening complications, in which a median survival drops to 2-4 years. Accordingly, the decompensation of LC is considered the most important stratification variable for the risk of death[1]. Decompensation of LC presents as acute decompensation in a portion of patients with the development of one or more major complications and is accompanied by high mortality. In many other patients, its characteristic signs are usually slow-progressing ascites or mild grade 1-2 hepatic encephalopathy or jaundice not requiring hospitalization[2].

The European Association for the Study of the Liver (EASL)-CLIF Consortium CANONIC study established diagnostic criteria for acute-on-chronic liver failure (ACLF) and introduced the concept of acute decompensation as a distinct clinical presentation of decompensation of LC defined by the acute development of more than one major complication: (1) Acute (for less than 2 wk) development of grade 2 or 3 ascites. This may be the first or a new episode of ascites; (2) Acute hepatic encephalopathy, which is manifested by a sudden change in the mental status of a patient with no previous cognitive impairment and no signs of acute neurological disease. This may be the first or a new episode of hepatic encephalopathy; (3) Acute gastrointestinal bleeding from the upper and/or lower gastrointestinal tract of any etiology; and (4) Spontaneous bacterial peritonitis (SBP), spontaneous bacteremia, urinary tract infection, pneumonia, cellulite, as well as any other type of acute bacterial infection[3].

The cause of acute decompensation of LC can be both exogenous factors (*e.g.*, bacterial infections, alcohol abuse, *etc*) and endogenous factors (*e.g.*, progressive liver disease, translocation of intestinal bacterial immunogenic material to the systemic circulation)[4]. Its most severe form (ACLF) according to the definition of the American College of Gastroenterology is a potentially reversible condition in patients with chronic liver disease with or without LC that is associated with the potential for multiple organ failure and mortality within 3 mo in the absence of treatment of the underlying liver disease, liver support, or liver transplantation. The severity of organ failure may be assessed by the EASL-CLIF sequential organ failure assessment score or North American Consortium for the Study of End-Stage Liver Disease organ failure score[5].

The first investigation derived from the PREDICT study group of the EASL-CLIF Consortium uncovered that acute decompensation of LC without ACLF is a heterogeneous condition with three different clinical courses and two major pathophysiological mechanisms: Systemic inflammation and portal hypertension. The first clinical course includes patients who develop ACLF and have an extremely high short-term mortality rate, termed pre-ACLF. The second clinical course includes patients with unstable decompensated LC who require frequent hospitalizations unrelated to ACLF and is associated with a lower mortality risk than pre-ACLF. The third clinical course includes patients with stable decompensated LC who rarely require hospital admission and have a much lower 1-year mortality risk.

Each clinical course of acute decompensation of LC differs significantly regarding the grade of systemic inflammation and the severity of portal hypertension. A high grade of systemic inflammation at admission with exacerbation during follow-up is observed in pre-ACLF. A low grade of systemic inflammation at admission with subsequent steady course is observed in patients with unstable decompensated LC. A low grade of systemic inflammation at admission with subsequent improvement is observed in patients with stable decompensated LC. A high grade of portal hypertension is observed in patients with unstable decompensated LC. A low grade of portal hypertension is observed in pre-ACLF and stable decompensated LC[6].

The aim of the second investigation derived from the PREDICT study group of the EASL-CLIF Consortium was to analyze and characterize the precipitants leading to acute decompensation of LC without ACLF or with ACLF. Of all the potential precipitants explored, only four (proven bacterial infections, severe acute alcoholic hepatitis, gastrointestinal bleeding associated with shock, and toxic encephalopathy) fulfilled the diagnostic criteria of precipitants. Proven bacterial infections and severe alcoholic hepatitis were present in the absolute majority (> 96%) of the patients. However, no precipitating event could be identified in two-thirds of acute decompensation of LC without ACLF patients and in one-third of acute decompensation of LC with ACLF patients. These data suggest that acute decompensation of LC without ACLF develops more frequently in the context of endogenous mechanisms (*e.g.*, progressive liver disease, bacterial translocation). The prevalence and number of precipitants increased with the severity of the acute decompensation sub-phenotype form stable decompensated LC/unstable decompensated LC to pre-ACLF and ACLF, which were also directly related to clinical course severity and short-term mortality in patients with acute decompensation of LC. These data, therefore, strongly suggest that specific preventive and therapeutic approaches for these precipitants must improve outcomes in decompensated LC[7].

Current therapeutic strategies in acute decompensation of LC provide the removal of the precipitants, the treatment of specific complications, as well as intensive monitoring and support of vital body functions[8]. Liver transplantation may be a successful treatment option for some of the most severe ACLF patients, but its implementation is usually associated with high costs and worse survival compared to "standard" elective surgery[9].

Progress in understanding the underlying molecular mechanisms has led to the search for new interventions, drugs, and biological substances that can affect key links in the pathogenesis of acute decompensation in LC, for example the impaired gut-liver axis and associated systemic inflammation [10]. Given that particular alterations in the composition and function of gut microbiota play a crucial role here, this review summarized the investigations that describe the theoretical foundations and therapeutic potential of gut microbiota modulation in acute decompensation of LC.

LITERATURE SEARCH

This review provided an overview of the current knowledge of the therapeutic possibilities of gut microbiota modulation in acute decompensation of LC. The PubMed and Embase databases, the Web of Science platform, the Google Scholar retrieval system, the Cochrane Database of Systematic Reviews, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/), and the reference lists from related articles were used to search for relevant publications. Articles corresponding to the aim of the review were selected for 2003–2023 using the keywords: "liver cirrhosis," "acute decompensation," "acute-on-chronic liver failure," "pathogenesis," "therapy," "gut microbiota," and "modulation." The investigations that described the theoretical foundations and therapeutic potential of gut microbiota modulation in acute decompensation of LC were included.

SYSTEMIC INFLAMMATION AS A MAIN DRIVER OF ACUTE DECOMPENSATION IN LC

One of the leading hypotheses in recent years suggests that the main driver of acute decompensation and concomitant multiple organ failure in LC is systemic inflammation. Its cause may be the "spill over" of damage-associated molecular patterns, cytokines, and immune regulatory cells from the chronically inflamed liver and potential other inflamed tissue sites to the systemic circulation. Additionally, pathogen-associated molecular patterns (PAMPs), namely bacterial and bacterial products (in particular, the lipopolysaccharides of the cell wall of Gram-negative bacteria), due to pathological translocation from the intestinal lumen through the portal vein, reach the cirrhotic liver where they may be ineffectively cleared by Kupffer cells or shunted through vascularized septae into the systemic circulation, contributing to systemic inflammation (Figure 1). Over time, immune tolerance may develop, which is characterized by accumulation in the systemic circulation of immune cells with immune suppressive or immune regulatory properties, along with high serum levels of proinflammatory and anti-inflammatory cytokines, damage-associated molecular patterns, and PAMPs. Additionally, with further disease progression to ACLF, cells with a reduced capacity to repel microbial challenges appear in the systemic circulation, which increases the risk of infectious complications and sepsis[11].

Once the first episode of acute decompensation of LC develops, systemic inflammation follows a chronic course, with transient episodes of reactivation caused by exogenous proinflammatory factors or to bursts of bacterial translocation. Repeated episodes of acute decompensation during the clinical course of decompensated LC develop in the setting of reactivation of the immune system. The prognosis of patients with acute decompensation of LC associated with moderate, non-progressive systemic inflammation depends on the severity of portal hypertension. Patients with severe portal hypertension frequently develop an unstable clinical course, requiring frequent hospital readmission, and significant

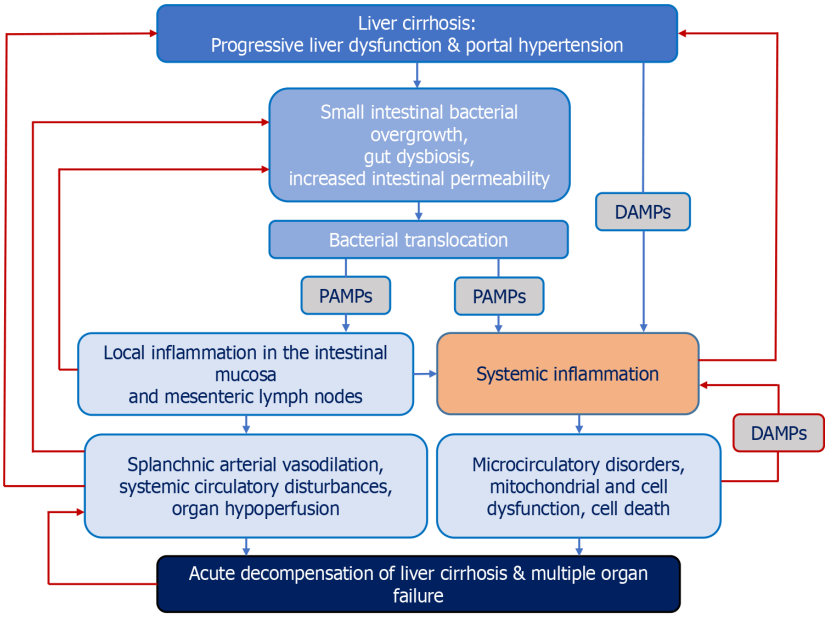

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Figure 1 Endogenous mechanisms of acute decompensation and concomitant multiple organ failure in liver cirrhosis. DAMPs: Damage-associated molecular patterns; PAMPs: Pathogen-associated molecular patterns.

short-term and long-term mortality. In contrast, if portal hypertension is moderate, systemic inflammation improves after the episode of acute decompensation of LC, patients develop a benign stable course, and long-term mortality is low[12].

THE ROLE OF GUT MICROBIOTA IN THE PATHOGENESIS OF ACUTE DECOMPENSATION IN LC

The alteration of gut microbiota composition in acute decompensation of LC creates prerequisites for disruption of the gut-liver axis, and bacterial translocation contributing to systemic inflammation is based on small intestinal bacterial overgrowth (SIBO), gut dysbiosis, and increased permeability of the intestinal epithelial barrier[13].

SIBO, which is characterized by an excessive number of bacteria in the small intestine (≥ 10^3 colony-forming units/mL) with a predominance of Gram-negative aerobic and anaerobic species, occurs in about half of the patients with LC, but the mechanism of its development has not been definitively established. One of the possible reasons may be the slowing down of orocecal transit[14]. However, the causal relationship between these pathophysiological conditions remains unclear. In some studies, a more pronounced slowing down of orocecal transit was observed in patients with Child-Turcotte-Pugh (CTP) class B and C LC with hepatic encephalopathy, which was explained by the autonomic neuropathy, metabolic derangements due to portosystemic shunting, and SIBO[15].

Because gastric acid is an important barrier that prevents bacterial colonization of the stomach and small intestine, it is assumed that proton pump inhibitor therapy may promote SIBO through chronic acid suppression and subsequent hypochlorhydria. However, a meta-analysis of 19 studies demonstrated that proton pump inhibitor therapy was significantly associated with a moderately increased risk of SIBO (odds ratio: 1.71, 95% confidence interval: 1.20-2.43)[16]. The immune system also plays a role in the genesis of SIBO, as evidenced by the high prevalence of SIBO in patients who have immunodeficiency. Besides, immunoglobulin A content on the duodenum and jejunum mucosa has been shown to be significantly increased in patients with SIBO[17].

Gut dysbiosis in LC is manifested by an unfavorable change in the balance of autochthonous species of microorganisms with a reduction in symbiont bacteria belonging to the Firmicutes phylum (*e.g.*, the Ruminococcaceae and Lachnospiraceae families, *etc*.) and growth in pathobiont bacteria of the Bacteroidetes and Actinobacteria phyla[18]. These changes largely depend on the etiology of LC and are aggravated in its decompensated stage. For example, they were the most significant in patients with alcoholic LC, who had the highest content of bacteria of the Enterobacteriaceae and Halomonadaceae families and the lowest content of bacteria of the Lachnospiraceae, Ruminococcaceae, and Clostridiales Incertae Sedis XIV families, which was accompanied by an exorbitant level of endotoxemia[19]. Note that the bacteria of the Enterobacteriaceae family express a powerful immunostimulating endotoxin and are the main pathogens involved in the pathogenesis of SBP[20]. In a study by Shu *et al*[21], in patients

with hepatitis B virus-related LC, the most common phyla of bacteria were Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia, together constituting 92.1% of the total number of microorganisms studied. Patients with compensated LC had a high relative abundance of bacteria of the genus *Faecalibacterium spp*. and the Ruminococcaceae family, whereas with decompensated LC, bacteria of the genus *Streptococcus spp*. and the Enterobacteriaceae family prevailed.

In a prospective study by Solé *et al*[22], patients with LC had a significant decrease in gene and metagenomic species diversity compared to healthy subjects. This was associated with disease stages and was especially noticeable in patients with ACLF and persisted after antibiotic therapy. ACLF was accompanied by a significant increase in *Enterococcus spp*. and *Peptostreptococcus spp*. and a decrease in some autochthonous bacteria. Gut microbiome alterations correlated with the model for end-stage liver disease (MELD) and CTP scores and multiple organ failure and were associated with some complications, especially hepatic encephalopathy and infections. Additionally, the gut microbiome predicted 3-mo survival with good stable predictors. Functional analysis showed that patients with LC had enriched pathways related to ethanol production, γ-aminobutyric acid metabolism, and endotoxin biosynthesis.

According to a study by Philips *et al*[23] pathogenic genera of bacteria in gut microbiota, in particular, *Leptotrichia spp*., *Neisseria spp*., and *Erwinia spp*., were predominant in patients with decompensated LC with infection, and their survival correlated with the presence of microorganisms with high functional propionate metabolism, for example, bacteria of the genus *Megamonas spp*.

Bajaj *et al*[19] developed a quantitative index to describe microbiome alterations accompanying LC based on the ratio of "good *vs* bad" taxa abundance [cirrhosis dysbiosis ratio (CDR)]. It is designed to predict the course of LC and assess the risk of possible complications. CDR is calculated using the formula:

CDR = [Lachnospiraceae (%) + Ruminococcacceae (%) + Veillonellaceae (%) + Clostridiales Incertae Sedis XIV (%)]/[*Bacteroides spp.* (%) + Enterobacteriaceae (%)].

The authors found that a low CDR was associated with death and organ failure within 30 d.

In a prospective study by the North American Consortium for the Study of End-Stage Liver Disease, including hospitalized patients with LC across North America, the CDR was lower in subjects who developed ACLF, especially among those with renal failure. Taxa belonging to the Proteobacteria phylum (Enterobacteriaceae, Campylobacteriaceae, and Pasteurellaceae) and Firmicutes phylum (Enterococcaceae and Streptococcaceae) were associated with the development of negative outcomes, whereas other Firmicutes members (Lachnospiraceae and Clostridiales) reduced the risk of negative outcomes. Changes in the microbiota were associated independently on logistic regression analyses with extrahepatic organ failure, transfer to intensive care, ACLF, and death[24].

To study the influence of gut dysbiosis on prognosis in LC, Maslennikov *et al*[25] modified CDR by placing "bad" bacteria in the numerator and "good" bacteria in the denominator (MDR)[25]:

MDR = [Bacilli (%) + Proteobacteria (%)]/[Clostridia (%) + Bacteroidetes (%)].

Their case-control study included 48 patients with LC and 21 healthy controls. Patients with an MDR greater than the median indicated the group with severe dysbiosis. The other patients were in the non-severe dysbiosis group. The follow-up period was 4 years. The mortality rate of patients with severe dysbiosis was significantly higher than that of patients with non-severe dysbiosis. The abundance of Enterobacteriaceae, Proteobacteria, and Lactobacillaceae was increased and the abundance of Firmicutes and Clostridia was reduced in the deceased patients compared with survivors. The abundance of Bacilli, Enterococcaceae, and Lactobacillaceae was higher and the abundance of Clostridia was lower in those who died during the 1st year of follow-up compared with those who survived the 1st year. The abundance of Enterobacteriaceae and Proteobacteria was higher in those who died in the second to 4th year of follow-up compared with survivors.

The cause of gut dysbiosis in LC is not fully understood. One of the key theories explains its presence by depletion of the pool of bile acids due to a decrease in their synthesis and secretion by hepatocytes. Bile acid synthesis is regulated mainly through the activation of nuclear receptors, in particular the farnesoid X receptor (FXR), which also induces genes affecting intestinal permeability and inflammation, preventing bacterial translocation in experimental LC[26]. Bile acids have both direct and indirect antimicrobial effects through the modulation of FXR activity, which is important for the homeostasis of the epithelial and gut-vascular barrier. Colonic microbial groups are responsible for the deconjugation and 7α-dehydroxylation of bile acids, and it is hypothesized that the presence of microbe toxic bile acids (particularly deoxycholic acid) in the intestine is a factor that keeps undesirable microbial populations under control[27]. The insufficient content of primary bile acids in feces decreased in 7α-dehydroxylating bacteria belonging to the Firmicutes phylum, especially the genera *Blautia spp*. and *Ruminococcus spp*. Their deficiency in the small intestine causes overgrowth of proinflammatory pathogenic bacteria belonging to the Proteobacteria phylum, in particular the Enterobacteriaceae family, which induces the release of markers of intestinal inflammation and exacerbates necroinflammatory changes in liver tissues. This triggers a positive feedback mechanism leading to additional inhibition of bile acid synthesis[28]. On the contrary, oral administration of conjugated bile acids to rats with a model of CCl4-induced LC and ascites significantly reduced the bacteria in the ileum (especially *Escherichia coli* and *Enterococcus spp*.) to levels comparable to those in healthy rats, decreased the SIBO, bacterial translocation, and endotoxemia[29].

Increased permeability of the intestinal epithelial barrier is associated with both gut dysbiosis[30] and microcirculatory disorders in LC that change the barrier properties of the intestinal mucosa, which include mechanical, biological, immune, and chemical protection factors[31]. Intestinal mucosa and intercellular junctions among epithelial cells form a layer that allows selective passage of the toxins and bacterial products. Intestinal epithelial cells produce mucus, which forms a thick layer on the mucosa and prevents bacterial translocation. Mucous secretions are rich in immunoglobulin A, which neutralizes toxins and microorganisms and prevents their adhesion and colonization. Bile acid secretion also plays a role in intestinal permeability by affecting the intestinal mucosa and by neutralizing endotoxin[32].

In LC, the thickness of the intestinal mucosa is decreased with the loss of mucus-producing goblet cells. The ultrastructural changes of the mucosa, contributing to increased permeability of the intestinal epithelial barrier, are characterized by atrophy, edema, and inflammatory infiltration of the lamina propria, fibromuscular proliferation, expansion of the space between neighboring cells, a reduction in the number of short but thicker microvilli, and a decrease in the villi/crypt ratio. These disorders are associated with a diminution in the expression of the tight junction proteins, including occludin and claudin-1, in the intestinal mucosa. Additionally, irregularities of the glandular epithelia, loss of the normal cylindrical shape, edematous villi, and loosening of the mucous membrane were revealed. High levels of lipid peroxidation markers in enterocytes led to mitochondrial dysfunction and cellular instability[33].

The increased stimulation of gut-associated lymphoid tissue leads to the persistent activation of monocytes, dendritic cells, and T lymphocytes both in the intestinal mucosa and mesenteric lymph nodes and to the consequent production of proinflammatory and anti-inflammatory cytokines. Local inflammatory disorders can be a trigger for systemic inflammation because of immune cells entering the systemic circulation. This is facilitated by a violation of the production of intestinal antimicrobial peptides, in particular α-defensins and Reg3 lectins, a decrease in the ability to bind and neutralize bacterial endotoxin by albumin, lipopolysaccharide-binding protein, high-density lipoproteins, low-density lipoproteins, very low-density lipoproteins, chylomicrons, apolipoproteins, as well as dysfunction of the immune system in patients with LC[34].

The persistence of systemic inflammation leads to a progressive failure of the immune response similar to a condition of immunodeficiency. The immune dysregulation in patients with LC can be defined as a "dysbiotic immune-inflammatory disorder" characterized by abnormal local (gut and liver) and systemic inflammation, triggered by an impaired immune response to gut-derived antigens. The main feature of cirrhotic dysbiotic immune-inflammatory disorder is a perpetual immunologic activation, which involves all the immune cells (neutrophils, monocytes, T and B lymphocytes) that exhibit activation and costimulatory markers.

At the molecular level, the recognition of PAMPs by Toll-like receptors activates MyD88-dependent and MyD88-independent signaling pathways, leading to the activation of nuclear factor kB, production of inflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, and interferon-β], chemokines [keratinocyte chemoattractant (CXCL1), MIP-2 (CXCL2), MCP-1 (CCL2), RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4)], nitric oxide, and reactive oxygen species[35].

The association of Toll-like receptor gene polymorphisms with a decrease in the inflammatory response was established, which further increases the load of circulating bacterial antigens that modulate the immune response and contribute to the development of complications[36]. Cytosolic NOD-like receptors (NLRs) are also involved in this process. The NLRP3 inflammasome formed after the oligomerization of the NLRP3 protein activates caspase 1, which cleaves pro-IL-1β and pro-IL-18, followed by the formation of proinflammatory cytokines IL-1β and IL-18[37].

A cascade of molecular events arising from dysbiotic immuno-inflammatory disorders leads to the enhanced phagocytic activity, vascular endothelial injury, synthesis of acute phase proteins by the liver, chemotaxis of leukocytes to the sites of inflammation (mainly the liver), and activation of leukocytes at the systemic level[38]. This in itself worsens bacterial translocation and contributes to the formation of a vicious circle, which can aggravate the pathological process associated with acute decompensation of LC and predispose to the development of its characteristic complications.

GUT MICROBIOTA AS A POTENTIAL TARGET FOR PROPHYLAXIS AND THERAPY OF ACUTE DECOMPENSATION IN LC

In accordance with the current recommendations of the EASL, one of therapeutic strategy that prevents disease progression in patients with decompensated LC should be aimed to improve the microbiome abnormalities and bacterial translocation to ameliorate the impaired gut-liver axis[39]. In this regard, a potential target for therapy may be the gut microbiota, which is the main regulator of bacterial translocation and systemic inflammation[40].

Antibiotics

The use of non-absorbable or poorly absorbable oral antibiotics is an obvious solution aimed at countering bacterial translocation. They affect the gut microbiota with rare side effects and a favorable long-term safety profile and are recommended as primary and secondary prevention of bacterial infections and treatment of hepatic encephalopathy in patients with decompensated LC[41].

Selective decontamination of the intestine with norfloxacin can contribute to a significant reduction in bacterial translocation. In a study by Albillos *et al*[42], this was manifested by a reduction in the serum levels of lipopolysaccharide-binding protein, soluble CD14, proinflammatory cytokines TNF-α, IL-12 and interferon-γ, as well as the metabolite nitric oxide. In a multicenter, randomized, prospective, double-blind, placebo-controlled trial in parallel groups (NORFLOCIR), including 291 patients with CTP class C LC, the administration of norfloxacin at a dose of 400 mg once daily for 6 mo significantly decreased the incidence of any and Gram-negative bacterial infections without growth infections caused by *Clostridium difficile* or multiresistant bacteria and an increase in survival in patients with ascites fluid protein concentrations < 15 g/L[43].

At the same time, long-term use of norfloxacin increased gut microbiota resistance to fluoroquinolones[44]. Given this, a semisynthetic broad-spectrum antibiotic rifaximin was proposed as an alternative. Rifaximin belongs to the family of naphthalene-ringed ansamycins (rifamycins group) and has a low risk of bacterial resistance. In a randomized controlled trial (RCT) involving 36 patients with decompensated LC with ascites and mean values of the MELD score of 12 ± 3.9, after 4 wk of treatment with rifaximin at a dose of 550 mg twice a day, circulating markers of inflammation, including TNF-α, IL-6, IL-10, IL-18, stromal cell factor-1α, transforming growth factor β1, and high sensitivity C-reactive protein, were unaltered. Rifaximin altered abundance of bacterial taxa in blood marginally, only a decrease in the Pseudomonadaceae family was observed. In feces, rifaximin decreased the bacterial richness but did not affect the particular species[45].

In an observational study involving 30 patients with decompensated LC after 4 wk of treatment with rifaximin at a dose of 1200 mg/d, there was an improvement in hyperammonemia and cognitive dysfunction, although no significant changes in the serum proinflammatory cytokine levels were observed. Rifaximin reduced the serum levels of ammonia, bacterial endotoxin, soluble CD163, and the D-mannose receptor. At the same time, the serum proinflammatory cytokine levels remained the same. Gut microbial analysis revealed that the richness and complexity of species were unchanged, while the abundance of the genus *Streptococcus spp*. after treatment with rifaximin was reduced[46].

The current literature data do not provide a clear answer as to which of the antibiotics is more effective in preventing bacterial translocation in patients with decompensated LC. Nevertheless, in a randomized, double-blind, placebo-controlled trial by Kulkarni *et al*[47], primary prophylaxis with oral norfloxacin (400 mg/d for 30 d) effectively prevented bacterial infections in patients with ACLF. Furthermore, a systematic review and meta-analysis of 17 RCTs showed that rifaximin is useful for both primary and secondary prevention of SBP, whereas norfloxacin daily and alternate norfloxacin and rifaximin are useful for primary prophylaxis[48].

Probiotics

A scientific basis for the use of probiotics in the treatment of liver diseases is their ability to correct gut dysbiosis, elevate the production of short-chain fatty acids, and reduce the increased permeability of the intestinal epithelial barrier[49]. The therapeutic potential of probiotics in LC has been studied in both experimental and clinical studies. For example, oral administration of a combined probiotic VSL#3 containing 8 different strains (*Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, *Streptococcus thermophilus*) to rats with different models of LC led to stabilization in the intestinal epithelial barrier, reduction of bacterial translocation, and decrease in severity of endotoxemia and systemic inflammation [50,51]. Oral administration of probiotics *Bifidobacterium pseudocatenulatum* CECT7765 to mice with a model of CCl4-induced LC was accompanied by an improvement in the integrity of the intestinal epithelial barrier and prevented bacterial translocation[52]. It also induced a morphologic, phenotypic, and functional transitional change towards an anti-inflammatory profile in blood-derived and ascitic fluid macrophages from patients with CTP class C LC as well as Kupffer cells from rats with a model of bile duct ligation-induced LC[53]. The combined use of probiotics containing *Clostridium butyricum* and *Bifidobacterium infantis* in patients with hepatitis B virus-related LC and minimal hepatic encephalopathy significantly decreased the pathogenic bacteria of the genus *Enterococcus spp*. and the Enterobacteriaceae family in gut microbiota as well as reduced the circulating levels of bacterial translocation markers and decreased the permeability and damage of the intestinal epithelial barrier[54].

Some RCTs have studied the effect of probiotics on gut microbiota in patients with LC. In one of them, the administration of the probiotic beverage Yakult 400, which contains *Lactobacillus casei* strain Shirota, twice a day during the first half of the 4-wk study contributed to the normalization of gut microbiota and improved liver function in patients with CTP class A alcoholic LC[55]. This probiotic was safe and effective in patients with cirrhosis (CTP score ≤ 10) who took it three times daily for 6 mo. It significantly reduced the plasma monocyte chemotactic protein-1, plasma IL-1β (alcoholic LC), IL-17a, and macrophage inflammatory protein-1β (non-alcoholic LC) compared to the placebo group. At the

same time, no significant differences in intestinal permeability, bacterial translocation, or metabolomic profile were observed[56].

Bajaj *et al*[57] showed that the administration of the probiotic *Lactobacillus rhamnosus GG* for 8 wk to patients with LC (mean values of the MELD score of 8.6 ± 2.2) and minimal hepatic encephalopathy was safe and well tolerated and reduced the serum levels of bacterial endotoxin and TNF-α, decreased the relative abundance of Enterobacteriaceae family, and increased the Clostridiales Incertae Sedis XIV and Lachnospiraceae families, without changes in cognitive dysfunction.

Daily intake for 6 mo of a probiotic powder containing eight different bacterial strains (*Bifidobacterium bifidum W23*, *Bifidobacterium lactis W52*, *Lactobacillus acidophilus W37*, *Lactobacillus brevis W63*, *Lactobacillus casei W56*, *Lactobacillus salivarius W24*, *Lactococcus lactis W19*, and *Lactococcus lactis W58*) by patients with cirrhosis (CTP score < 12) had a beneficial effect on immune function, but no effect on the permeability of the intestinal epithelial barrier and bacterial translocation was observed[58]. In addition, it increased the relative abundance of bacteria of the species *Faecalibacterium prausnitzii*, *Syntrophococcus sucromutans*, *Bacteroides vulgatus*, and *Alistipes shahii* and the genus *Prevotella spp*. compared to the placebo group. At the same time, the relative abundance of bacteria of the species *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, and *Lactobacillus casei* remained unchanged[59].

Thus, although in most studies the probiotic use in LC is associated with an improvement in gut microbiota profile, data concerning their impact on permeability of the intestinal epithelial barrier, bacterial translocation, and systemic inflammation are scarce and contradictory.

Fecal microbiota transplantation

In recent years, numerous studies have demonstrated the therapeutic possibilities of fecal microbiota transplantation (FMT) from healthy donors to patients with chronic liver diseases[60]. It is assumed that the effectiveness of FMT is associated with the creation of a competitive environment in the intestine due to non-pathogenic microorganisms and their production of antimicrobial substances, such as bacteriocins. In addition, the positive effect of donor fecal material on the gut virome and microbiota, the metabolism of short-chain fatty acids and some bile acids, as well as various immune mechanisms is not excluded[61]. Much attention has been paid to the use of FMT to treat hepatic encephalopathy in LC. At the same time, the issues of its effectiveness, safety, and tolerability, as well as methods of administration of donor fecal material (using enemas, colonoscopy, or in encapsulated form), the type and number of transplanted microorganisms necessary to obtain a positive result are discussed[62].

In the first open-label RCT involving 10 patients with LC (MELD score < 17) and recurrent hepatic encephalopathy, three frozen-then-thawed FMT units (90 mL total) instilled by enema and retained for 30 min eliminated antibiotic-induced dysbiosis. All patients showed an improvement in cognitive dysfunction, which may have been associated with an increase of the relative abundance of bacteria of the Lactobacillaceae and Bifidobacteriaceae families[63]. With further follow-up (12.9 ± 2.9 mo), no cases of hepatic encephalopathy were detected, and only 1 patient from this cohort required hospitalization. Microbiological analysis of the gut microflora showed an increase of relative abundance of bacteria of the Burkholderiaceae family and a decrease in the relative abundance of bacteria of the Acidaminococcaceae family, while the relative abundance of bacteria of the Lactobacillaceae and Bifidobacteriaceae families did not differ from the placebo group[64].

In a phase I RCT, the administration of 15 capsules with donor fecal microbiota to 10 patients with LC (MELD score < 17) and recurrent hepatic encephalopathy had a positive effect on cognitive dysfunction was safe and well tolerated. After 30 d of monitoring, there was an improvement in duodenal mucosal microbial diversity with higher Ruminococcaceae and Bifidobacteriaceae families and lower Streptococcaceae and Veillonellaceae families (P = 0.01). Reduction in the Veillonellaceae family was seen post-FMT in sigmoid (P = 0.04) and stool (P = 0.05). Duodenal E-cadherin (P = 0.03) and defensin A5 (P = 0.03) increased, while the IL-6 (P = 0.02) and serum levels of lipopolysaccharide-binding protein (P = 0.009) reduced post-FMT[65].

An important problem of FMT is the risk of severe infection transmission, which is especially significant in patients with weakened immunities[66]. For this reason, the United States Food and Drug Administration published a list of minimum requirements for screening and testing of fecal microbiota donors for the presence of multidrug resistant microorganisms in 2019[67].

The coronavirus disease 2019 pandemic has raised concerns about the possible transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in FMT. Although the genetic material of SARS-CoV-2, including the live virus, has been detected in the feces of patients with a new coronavirus infection even after the elimination of respiratory symptoms[68], no actual cases of infection through donor fecal material were reported. Stool testing for SARS-CoV-2 is not currently widely available. Nevertheless, experts advocate screening donors for the presence of symptoms of a new coronavirus infection with quarantine of their fecal material during further monitoring of the disease [69].

Obeticholic acid

Obeticholic acid is a semisynthetic bile acid that, in addition to bacteriostatic activity, is an agonist of FXR and thus can modulate the gut microbiota. For example, oral administration of obeticholic acid to rats with a model of CCl4-induced LC reduced the intestinal content of the genus *Enterococcus spp*.[70]

and decreased the bacterial translocation[71]. Besides, obeticholic acid prevented the increased expression of monocyte chemoattractant protein-1 following stimulation with TNF-α and lipopolysaccharides or TNF-α alone in liver sinusoidal endothelial cells and Kupffer cells in rats with a model of thioacetamide-induced LC[72]. In these studies, obeticholic acid had a beneficial effect on the production of antimicrobial peptides by ileum epithelial cells, the expression of the tight junction proteins, intestinal inflammation, and liver fibrosis.

At present, the therapeutic potential of obeticholic acid in LC has been primarily studied in experimental models, and for safety reasons its use in patients with decompensated LC is still considered premature.

Carbon nanoparticles

The newly developed carbon-based enterosorbent Carbalive™ (Yaq-001, Yaqrit Limited, United Kingdom) has a high absorption capacity for bacterial toxins and may be a new strategy to counteract changes in gut microbiota and translocation of bacterial products in patients with decompensated LC. It is non-absorbable carbon nanoparticles with a tailored bimodal distribution of porous domains within the macroporous range (> 50 nm) and microporous range (< 2 nm) and a vast surface area.

The biological significance of this is that in addition to binding smaller mediators such as indoles, acetaldehyde, *etc* carbon granules exhibit rapid adsorption kinetics for larger molecular weight factors, for example bacterial endotoxin, exotoxins, and cytokines. Yaq-001 was found to reduce liver injury, portal pressure, and lipopolysaccharide-induced reactive oxygen species production in an *in vivo* model of LC and ACLF[73]. Yaq-001 significantly increased the relative abundance of symbiont bacteria belonging to the Firmicutes phylum and decreased the relative abundance of pathobiont bacteria belonging to the Bacteroidetes phylum in fecal samples from rodents with a model of bile duct ligation-induced LC, despite the absence of a direct effect on bacterial growth kinetics[74]. In the first phase II multicenter, randomized, double-blind, placebo-controlled trial (CARBALIVE:634579), 14 patients with decompensated LC with diuretic-responsive ascites and mean MELD scores of 12.4 ± 0.9 received 4 g of Yaq-001 for 12 wk. Yaq-001 was safe, well tolerated, contributed to the restoration of intestinal eubiosis, and by affecting the permeability of the intestinal epithelial barrier weakened the severity of endotoxemia and systemic inflammation[75].

CONCLUSION

Given that particular alterations in the composition and function of gut microbiota play a crucial role in the pathogenesis of acute decompensation in LC, the study of the therapeutic possibilities of its modulation has emerged as one of the top concerns in modern hepatology. Despite the encouraging preliminary data, the majority of the suggested strategies have only been tested in animal models or in preliminary clinical trials; additional multicenter RCTs must demonstrate their efficacy in larger patient populations.

FOOTNOTES

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MINIREVIEWS

Morphological aspects of small-duct cholangiopathies: A minireview

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Abstract

The biliary system consists of intrahepatic and extrahepatic bile ducts lined by biliary epithelial cells (cholangiocytes). Bile ducts and cholangiocytes are affected by a variety of disorders called cholangiopathies, which differ in aetiology, pathogenesis, and morphology. Classification of cholangiopathies is complex and reflects pathogenic mechanisms (immune-mediated, genetic, drug- and toxin-induced, ischaemic, infectious, neoplastic), predominant morphological patterns of biliary injury (suppurative and non-suppurative cholangitis, cholangiopathy), and specific segments of the biliary tree affected by the disease process. While the involvement of large extrahepatic and intrahepatic bile ducts is typically visualised using radiology imaging, histopathological examination of liver tissue obtained by percutaneous liver biopsy still plays an important role in the diagnosis of cholangiopathies affecting the small intrahepatic bile ducts. To increase the diagnostic yield of a liver biopsy and determine the optimal therapeutic approach, the referring clinician is tasked with interpreting the results of histopathological examination. This requires knowledge and understanding of basic morphological patterns of hepatobiliary injury and an ability to correlate microscopic findings with results obtained by imaging and laboratory methods. This minireview describes the morphological aspects of small-duct cholangiopathies pertaining to the diagnostic process.

Key Words: Bile duct; Cholangiocytes; Cholangiopathy; Cholangitis; Liver biopsy; Histopathology

Core Tip: A wide range of non-neoplastic and neoplastic conditions affects the small intrahepatic bile ducts. Cholangiopathies account for significant morbidity and mortality and represent an important indication for liver transplantation in adult and paediatric populations. Pathogenesis of most cholangiopathies is complex, and likely involves both environmental and genetic factors. Understanding the underlying pathogenetic mechanisms, knowledge of basic morphological patterns, and an ability to correlate microscopic findings with results obtained by imaging and laboratory methods are important steps in forming an overall clinical picture and selecting the optimal therapeutic approach in patients with biliary diseases. Our minireview addresses some important morphological aspects of small-duct cholangiopathies relevant to the diagnostic process, and also provides a brief overview of the most clinically significant conditions in light of recent progress.

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INTRODUCTION

The biliary system is a three-dimensional complex of developmentally, anatomically, and functionally different ductal structures. The extrahepatic bile ducts are composed of the right and left hepatic ducts, their confluence, the common hepatic duct, and the common bile duct. The intrahepatic biliary tree is divided according to size into the large intrahepatic bile ducts (area and segmental) and the small intrahepatic bile ducts (interlobular and septal).

Septal bile ducts (> 100 μm in diameter) are lined by tall columnar cells with basal nuclei supported by a fibrous duct wall (Figure 1A). Interlobular bile ducts (15-100 μm) are thin-walled structures lined by cuboidal epithelial cells resting on a basal membrane (Figure 1B). Interlobular bile ducts are connected to a complex network by ductules (< 15 μm diameter), lined by low cuboidal cells, and the canals of Hering, which are partly composed of the biliary epithelium and partly of hepatocytes.

In humans, biliary epithelial cells (cholangiocytes) account for 3%-5% of the total liver cell mass. Cholangiocytes of the intrahepatic biliary tree are derived from the endodermal cells of the hepatic primordium, while epithelial cells lining the extrahepatic bile ducts derive from the caudal portion of the hepatic diverticulum[1,2].

Biliary epithelial cells along with a variety of receptors and transporters play important roles in the secretion and reabsorption of water, electrolytes, bile acids, and many other bile compounds. As well as modifying bile composition, cholangiocytes secreting mucin and HCO_3^- are important elements in the biliary self-defence system. In addition, biliary epithelial cells are involved in a wide range of physiological processes, including intracellular and intercellular signalling, liver regeneration, and immune-mediated reactions[3,4].

Bile ducts and cholangiocytes can be affected by a variety of disorders generally referred to as cholangiopathies. Under pathological circumstances, cholangiocytes can undergo morphological and functional changes, which differ according to the size of the affected segment of the biliary tree. Large bile duct disorders are primarily diagnosed by radiology imaging and liver biopsy is generally not required. However, in the case of small bile duct injuries, imaging methods are not adept at detecting alterations of the biliary tree. Therefore, histomorphological examination should be considered a relevant part of the diagnostic process.

To increase the diagnostic yield of a liver biopsy and arrive at an optimal therapeutic approach, the results of histopathological examination must be interpreted by the presiding clinician. This requires knowledge and understanding of the basic morphological patterns of hepatobiliary injury.

This minireview briefly addresses some important morphological aspects of small-duct cholangiopathies relevant to the diagnostic process, and also provides a brief overview of the most clinically significant conditions in light of recent progress.

CLASSIFICATION OF CHOLANGIOPATHIES

Biliary diseases are classified according to aetiological aspects, pathogenic mechanisms, and the predominant morphological pattern of bile duct injury.

Based on the underlying pathogenic mechanism, cholangiopathies can be classified as follows[5,6]: (1) Immune-mediated cholangiopathy; (2) genetic cholangiopathy; (3) drug- and toxin-induced cholangiopathy; (4) ischaemic cholangiopathy; (5) infectious cholangiopathy; and (6) neoplastic cholan-

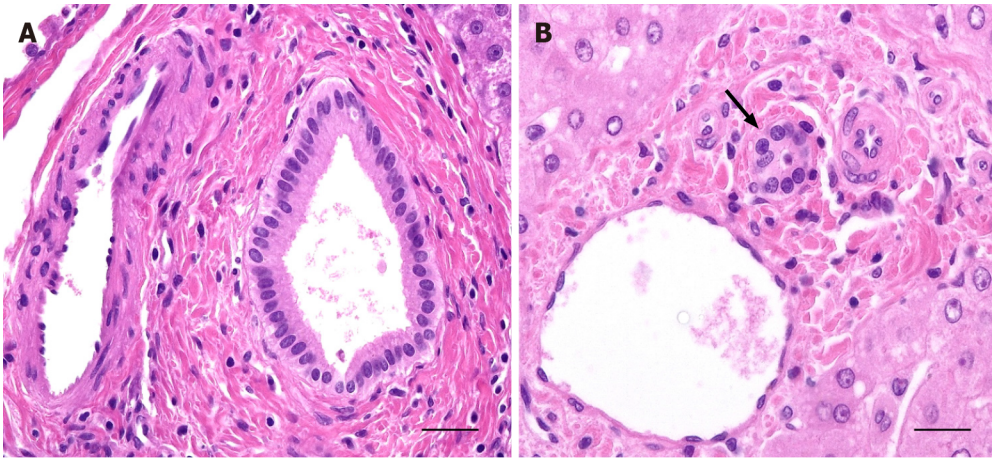

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Figure 1 Histology of small intrahepatic bile ducts. A: Septal bile duct lined by a columnar epithelium supported by a fibrous wall; B: Interlobular bile duct (arrow) lined by cuboidal epithelia. Haematoxylin and eosin; bar corresponds to 50 μm.

giopathy. From a morphological point of view, diseases that target bile ducts and cholangiocytes are categorised as either cholangitis (inflammatory bile duct injury) or cholangiopathy (non-inflammatory bile duct injury). Based on the predominant inflammatory cell type and the presence of associated periductal fibrosis, cholangitis can assume a suppurative (neutrophilic) form, predominantly infective, or a non-suppurative form, *e.g.* lymphocytic, pleomorphic, granulomatous, or sclerosing (Table 1)[5,6].

The most clinically important patterns of non-inflammatory bile duct lesions are ductal plate malformation, bile duct loss and ductopenia (vanishing bile duct syndrome), and – in a broader context – neoplastic biliary lesions[5].

GENERAL MORPHOLOGICAL ASPECTS OF SMALL-DUCT CHOLANGIOPATHIES

Several common features of cholangiopathies mainly affecting the small bile ducts have been observed. Considering that early histomorphological changes are often subtle and focal, they can be easily overlooked in a percutaneous liver biopsy. Early alterations secondary to impaired bile flow include focal mild portal oedema accompanied by mild periductal inflammation. Periportal ductular proliferation is commonly detectable at the periphery of some portal areas. Focal and mild juxtaportal copper and copper-associated protein depositions due to prolonged cholestasis can be highlighted by Schmorl's reaction and orcein or rhodanine staining. And although these changes are not pathognomonic, they can indicate a diagnosis of early-stage chronic cholangiopathy[7,8].

Morphological features of prolonged periportal bile salt accumulation (cholate stasis) can be accompanied by biliary interface activity, a complex reaction composed of periportal ductular proliferation with mild neutrophilic inflammation, aberrant cytokeratin 7 expression in hepatocytes (cholangiolar or ductular metaplasia), and varying degrees of fibrosis (Figure 2). Late stages of the disease are characterised by prominent cholate stasis with oedema and "feathery" degeneration of periportal hepatocytes containing Mallory-Denk hyaline inclusions and depositions of copper and copper-associated protein (Figure 2). This results in the formation of a signature "halo" effect at the peripheries of portal areas and septa (Figure 3A). Biliary-type fibrosis can also progress, with a typically uneven distribution of fibrous changes in the liver tissue. Periportal changes may be accompanied by bilirubinostasis in liver lobules, predominantly in the centrilobular zone (zone 3)[7,8,9].

Some cholangiopathies are associated with progressive small bile duct destruction and loss. Hepatic ductopenia, an uncommon but potentially serious cholestatic liver disease, is defined as a loss of the interlobular bile ducts in at least 50% of portal areas[7,10,11]. Ten portal tracts in a liver biopsy specimen are usually considered sufficient for an evaluation of bile duct loss. Vanishing bile duct syndrome is a rare condition in which progressive bile duct loss results in chronic cholestasis and ductopenia[10,11]. A heterogeneous group of conditions, comprising immune-mediated processes, drug- and toxin-induced hepatobiliary injury, ischaemia, infections, and some hereditary diseases, has been implicated in bile duct destruction (Table 2)[11,12].

Table 1 Morphological classification of cholangiopathies

Pattern of biliary injury		Disease
Cholangitis	Neutrophilic	Infection, sterile
	Lymphocytic	PBC, GVHD, allograft rejection
	Pleomorphic	AIH, PBC, DILI
	Granulomatous	PBC, sarcoidosis, DILI
	Sclerosing	PSC, IgG4-sclerosing cholangitis, DILI
Bile duct loss and ductopenia		See Table 2
Ductal plate malformation		See Table 3
Neoplastic		BilIN, IPN, cholangiocarcinoma

PBC: Primary biliary cholangitis; GVHD: Graft-versus-host disease; AIH: Autoimmune hepatitis; DILI: Drug induced liver injury; PSC: Primary sclerosing cholangitis; BilIN: Biliary intraepithelial neoplasia; IPN: Intraductal papillary neoplasia.

Table 2 Conditions associated with ductopenia

Infantile and childhood diseases	Bile duct paucity (syndromic/non-syndromic)
	Extrahepatic biliary atresia
	Progressive familial intrahepatic cholestasis
	Fibropolycystic disease
	Alpha-1 antitrypsin deficiency
Immune-mediated diseases	Primary biliary cholangitis
	Primary sclerosing cholangitis
	Chronic graft-versus-host disease
	Chronic hepatic allograft rejection
	Hepatic sarcoidosis
Vascular diseases	Ischaemic cholangiopathy
	Portal biliopathy
Infectious diseases	Ascending cholangitis
	Protozoal and parasitic infestations
Drug- or toxin-induced biliary injury	
Neoplastic diseases	Hodgkin's lymphoma
	Langerhans cell histiocytosis
	Systemic mastocytosis
Idiopathic	Idiopathic adulthood ductopenia

MORPHOLOGY OF SELECTED SMALL-DUCT CHOLANGIOPATHIES

The major histomorphological features of various small-duct cholangiopathies are briefly discussed below.

Immune-mediated bile duct injury

Primary biliary cholangitis: Primary biliary cholangitis (PBC) is an autoimmune disease that selectively affects the small intrahepatic bile ducts. Typical clinical features of PBC include marked female preponderance, middle-to-elderly age range, frequent association with other autoimmune disorders, pruritus, and skin hyperpigmentation. Increased activity of serum alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), elevated serum IgM, and the presence of M2-type antimitochondrial antibodies (AMA) are also commonly observed[13-15].

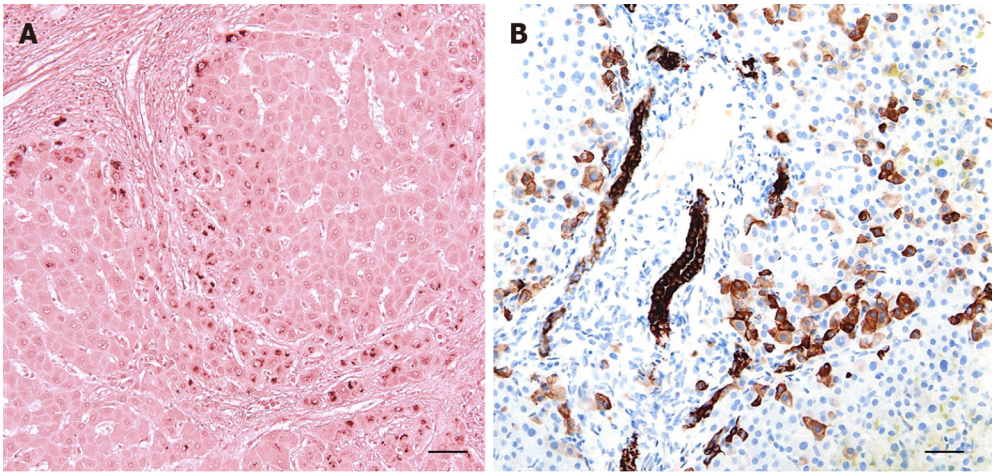

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Figure 2 Morphology of chronic cholestasis. A: Orcein-positive periseptal depositions of copper-binding protein in hepatocytes; B: Aberrant cytokeratin 7 immunoexpression on periportal hepatocytes. Bar corresponds to 100 μm (A) and 50 μm (B).

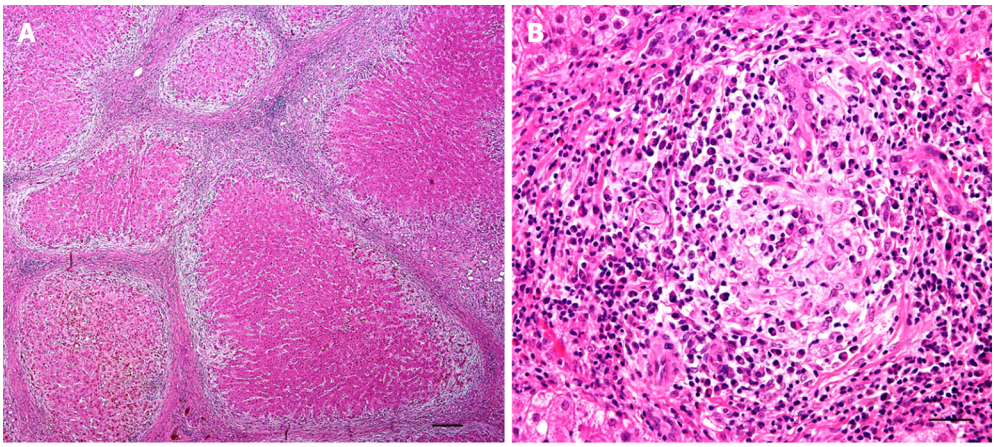

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Figure 3 Primary biliary cholangitis. A: Biliary-type cirrhosis with a signature "halo" at the peripheries of parenchymal nodules; B: Detail of portal tract with lymphoplasmacytic infiltrate and granulomatous destruction of the interlobular bile duct. Haematoxylin and eosin; bar corresponds to 500 μm (A) and 50 μm (B).

According to the classic histological systems proposed by Scheuer and Ludwig, microscopical changes are categorised into the following four stages[16,17]: Stage 1: Focal, destructive, lymphocytic and/or granulomatous cholangitis of the interlobular bile ducts (florid ductal lesion) with inflammation generally confined within portal tract boundaries (Figure 3B); Stage 2: Ongoing bile duct injury with portal tract expansion due to periportal ductular proliferation (biliary interface activity), inflammatory interface activity, and periportal fibrosis; Stage 3: Bridging portoportal fibrosis with persistent biliary interface activity and ongoing small bile duct loss; Stage 4: Cirrhosis with ductopenia and chronic cholestasis (cholate stasis) discernible by a periportal "halo" (Figure 3A).

The above classic staging systems are simple and easily reproducible. However, they do not reflect all of the morphological features of disease activity and progression that should be considered when determining the optimal therapeutic approach. In addition, the heterogeneous distribution of diagnostic changes in the liver parenchyma and the potential for sampling errors during percutaneous needle biopsy reduce their applicability and practical use. These shortcomings have been overcome by a novel complex system applicable to needle liver biopsy specimens proposed by Nakanuma *et al*[18,19]. Three components – fibrosis, bile duct loss, and chronic cholestasis – are used in this PBC staging system, while necroinflammatory activity of PBC is graded based on chronic cholangitis and hepatitis activity [18,19].

Apart from portal and portal-parenchymal interface changes, small cell changes in periportal hepatocytes and nodular regenerative hyperplasia (NRH) can occur during non-cirrhotic stages of PBC. NRH may explain the hepatomegaly in PBC and the development of clinically significant portal hypertension long before cirrhosis develops[20,21].

The following PBC variants have been recognised: AMA-negative PBC (autoimmune cholangitis) represents 5% of PBC cases. Subtle differences in the clinical, laboratory, and immunological features of AMA-negative PBC have been reported in a number of studies. However, the basic histopathological findings and responses to ursodeoxycholic acid are similar to those observed in AMA-positive patients [13,14].

PBC-AIH overlap syndrome is characterised by the features of both PBC and autoimmune hepatitis coexisting in a single patient. Diagnostic criteria for PBC-AIH overlap syndrome have been proposed by Chazouillères *et al*[22], while other guidelines have been issued by the International Autoimmune Hepatitis Group. These include the presence of at least two of three diagnostic features of PBC (1-3) and at least two of three diagnostic features of AIH (4-6)[23]: (1) GGT ≥ 5× upper limit of normal (ULN) or ALP ≥ 2× ULN; (2) positive AMA; (3) florid bile duct lesion on histology; (4) increased alanine transaminase (ALT) levels ≥ 5× ULN; (5) serum IgG levels ≥ 2× ULN or positive anti-smooth muscle antibody (SMA); and (6) moderate or severe lymphocytic interface activity on histology.

Nevertheless, as opposed to genuine overlap syndrome, most cases are best regarded as either PBC with unusually prominent inflammatory activity (PBC with hepatitis features) or as classical AIH with PBC-like bile duct injury.

Rare cases of overlapping features involving PBC and primary sclerosing cholangitis (PSC), IgG4-related sclerosing cholangiopathy, and sarcoidosis have been reported in the medical literature[14,22].

Small-duct PSC

PSC is a chronic cholestatic condition characterised by non-specific inflammatory fibrosis in bile duct walls of all sizes, with irregular areas of stricturing and beading on cholangiography. Unlike PBC, PSC can occur in infancy and childhood, has a male preponderance, and is closely associated with inflammatory bowel disease (IBD). An increased risk of hepatobiliary malignancy in PSC patients has also been observed[13,14,24,25].

PSC typically involves extrahepatic and large intrahepatic bile ducts with variable involvement of small ducts. Nonetheless, in 5%–10% of cases, the disease is confined to the small intrahepatic bile ducts (small-duct PSC or sdPSC)[24,25,26]. The aetiopathogenesis of sdPSC is poorly understood. A study by Naess *et al*[27] evaluated sdPSC components in a subset of patients with and without concomitant IBD. They found that patients with sdPSC and IBD may represent precursor lesions indicative of classic PSC, while sdPSC patients without IBD could point to a different biliary disease process.

Since a cholangiography is negative in sdPSC, histopathological evaluation of liver tissue specimens is usually required to establish a diagnosis. Although most studies have reported that sdPSC has a similar histopathological picture to large-duct PSC, its pathognomonic features may be subtle and randomly distributed within the liver tissue[7,24,26]. The distinctive features of PSC are fibro-obliterative lesions characterised by 'onion-skin' periductal fibrosis and replacement of the bile duct by a dense acellular fibrous scar (Figure 4). Biliary changes are frequently associated with mild portal tract oedema, low-grade periductal inflammatory infiltrate, and periportal ductular proliferation accompanied by juxtaportal copper and copper-binding protein deposition. As the disease advances, fibrous expansion of portal areas may progress to bridging septal fibrosis and eventual biliary-type cirrhosis[7,24,26].

Histopathological changes in PSC are divided into four stages (1-4) based on the same classification systems as proposed for PBC (see above).

Autoimmune sclerosing cholangitis (PSC-AIH overlap syndrome) is a variant syndrome characterised by features of sclerosing cholangitis and AIH serology[15,23,28]. Importantly, biliary features detected by histopathological examination may be the first indication for biliary tree imaging in patients originally diagnosed with uncomplicated AIH. The syndrome is more common in children and adolescents, with these groups also displaying higher prevalence of sdPSC[7,15,28].

IgG4-related sclerosing cholangitis

IgG4-related sclerosing cholangitis is now considered a biliary manifestation of systemic IgG4-related disease. This condition is commonly associated with IgG4-related lesions in other organs, most often with type 1 autoimmune pancreatitis[29,30]. The affected extrahepatic, hilar and perihilar ducts show diffuse and uniform tube-like thickening on gross examination. Histological characteristics of large duct lesions are transmural inflammation, obliterative phlebitis, and heavy lymphoplasmacytic infiltration with a predominance of IgG4-positive cells and abundant eosinophilic leukocytes (Figure 5)[29,30]. In up to 30% of patients, intrahepatic disease involving the small bile ducts is detectable by liver biopsy. Morphological findings include plasma cell-rich portal inflammation and portal fibrosis, interlobular bile duct damage, lobular inflammation, and features of cholestasis with periportal copper-associated protein deposition. A distinctive portal-based fibroinflammatory nodule composed of inflammatory cells and fibroblasts was observed in 50% of liver biopsies obtained from patients with IgG4-related sclerosing cholangitis[30,31,32]. While differentiating the condition from PSC by needle biopsy is challenging, the presence of more than ten IgG4+ plasma cells on liver biopsy can serve as a diagnostic aid[30,31].

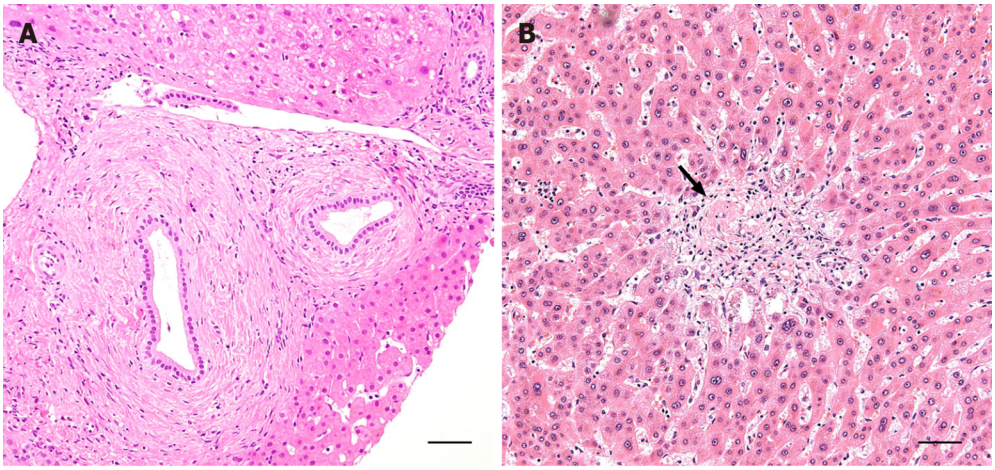

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Figure 4 Primary sclerosing cholangitis. A: Concentric periductal lamellar fibrosis; B: Complete fibrous obliteration of the interlobular duct (arrow). Haematoxylin and eosin; bar corresponds to 100 μm.

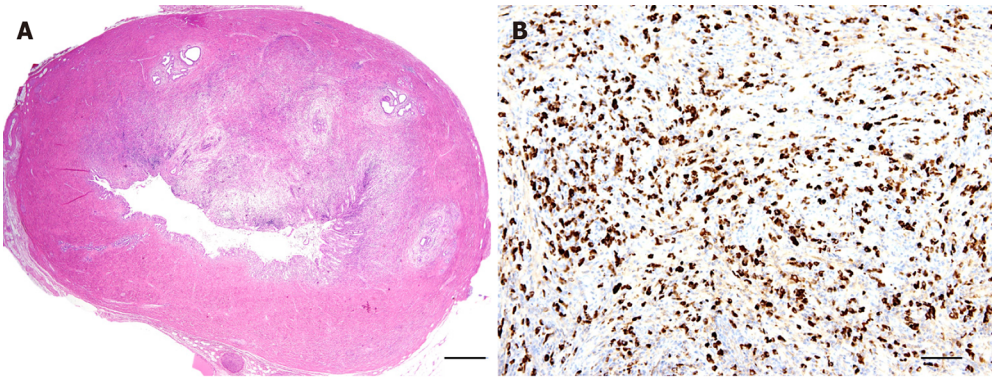

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Figure 5 Morphology of IgG4-related sclerosing cholangiopathy. A: Marked fibroinflammatory thickening of the bile duct wall; B: Increased numbers of IgG4-positive plasma cells. Haematoxylin and eosin (A), IgG4 immunohistochemistry (B). Bar corresponds to 1000 μm (A) and 100 μm (B).

Rejection cholangiopathy and biliary lesions in graft-versus-host disease

Cholangiocytes and small interlobular bile ducts are targets of an immune reaction associated with liver allograft rejection and graft-versus-host disease (GVHD)[5,33].

Biliary lesions in acute T cell-mediated rejection are characterised by periductal and intraepithelial lymphocytic infiltration, degenerative changes to biliary epithelial cells with cytoplasmic vacuolisation, increased N:C ratios, disordered nuclear polarity, and eventual luminal disruption (Figure 6A). Senescence-related changes to biliary epithelial cells (eosinophilic cytoplasmic transformation, uneven nuclear spacing, nuclear hyperchromasia) and progressive interlobular bile duct loss indicate chronic (ductopenic) rejection (Figure 6B)[33-35].

Immune-mediated small bile duct injury, degenerated dysplastic-like cholangiocytes, and progressive bile duct destruction are the most characteristic histological features of GVHD, a frequent complication of haematopoietic cell transplantation. Lymphocytic infiltration of the biliary epithelium in GVHD is usually minimal to mild[36].

GENETIC CHOLANGIOPATHIES

Genetic factors are variably implicated in most cholangiopathies. In addition to ductal plate malformation (hereditary fibropolycystic disease), neonatal sclerosing cholangitis, and various conditions within the spectrum of familial intrahepatic cholestasis, cholangiopathy can also occur in cystic fibrosis, a multisystemic disease caused by a homozygous or compound heterozygous mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene[37]. Alpha-1 antitrypsin deficiency (AATD) is an autosomal recessive storage disease caused by pathogenic mutations in the *SERPINA1* gene. Besides pulmonary emphysema, AATD can manifest as a progressive cholestatic liver

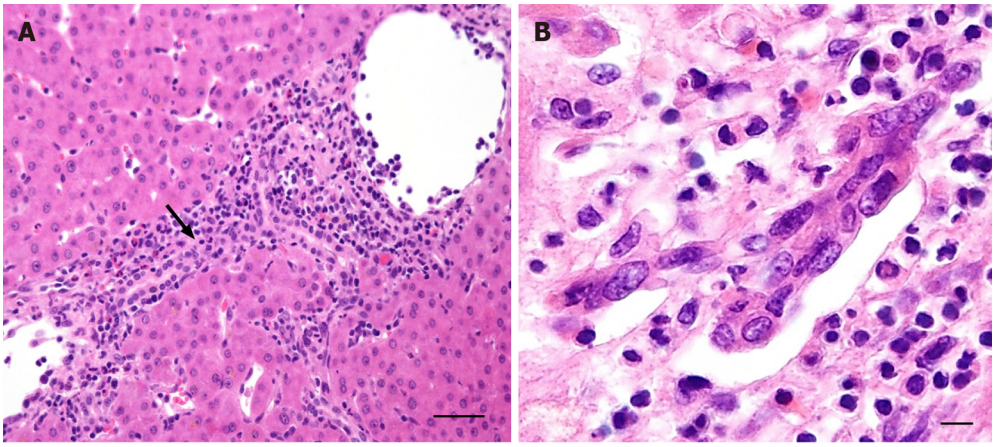

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Figure 6 Rejection cholangiopathy. A: Inflammatory damage of interlobular bile duct (arrow) in acute T cell-mediated rejection; B: Senescence-related changes of the interlobular bile duct in chronic rejection. Haematoxylin and eosin; bar corresponds to 50 μm (A) and 25 μm (B).

disease involving hypoplasia of the small bile ducts, mostly occurring in paediatric patients[38].

Ductal plate malformation

Ductal plate malformation is a common feature in ciliopathy-associated liver diseases, characterised by a spectrum of biliary hamartomatous lesions, segmental bile duct dilatations and cysts. All of the above conditions stem from aberrant remodelling of the embryonal ductal plate (Figure 7A)[39,40]. Liver disease is often associated with the involvement of other organs, mainly the kidneys. Over the past decade, a number of genes (and their corresponding protein products) involved in several of these disorders have been identified (Table 3)[40,41].

Alagille syndrome

Alagille syndrome (ALGS) is an autosomal dominant multisystem disorder accompanied by severe cholestasis due to congenital maldifferentiation of the intrahepatic bile ducts. The syndrome is caused by mutations in the *JAG1* gene, which encodes the intercellular signalling protein JAGGED1 (type 1 ALGS), and, rarely, the *NOTCH2* gene (type 2 ALGS)[42,43]. Common manifestations include paucity of the intrahepatic bile ducts with obstructive-type cholestasis, skeletal abnormalities (butterfly-like vertebrae), congenital heart disease (usually peripheral pulmonary stenosis), ocular anomalies, and facial dysmorphism[42,44].

ABCB4 deficiency-associated cholangiopathy

ATP-binding cassette (ABC) subfamily B member 4 (ABCB4), also known as multidrug resistance protein 3 (MDR3), is a membrane-associated transport protein. Almost exclusively expressed in the liver, ABCB4 is principally involved in biliary phospholipid secretion[45]. The *ABCB4* alteration has deleterious effects on the hepatobiliary system, mostly caused by toxic bile with a potent detergent and lithogenic profile. The morphological spectrum of biliary lesions connected with ABCB4/MDR3 deficiency varies widely. The most commonly associated conditions are gallbladder disease-1 (GBD1), also known as low phospholipid-associated cholelithiasis (LPAC) syndrome, secondary sclerosing cholangitis (characterised by fibro-obliterative lesions and progressive small bile duct loss), and adult biliary-type liver fibrosis/cirrhosis[46,47].

GBD1 (LPAC syndrome) should be suspected in patients with symptomatic cholelithiasis and at least one of the following criteria: under 40 years of age at onset of symptoms; recurrence after cholecystectomy; intrahepatic sludge or microlithiasis with spindle-shaped dilatations of the intrahepatic bile ducts on cholangiography; familial history of cholelithiasis in first-degree relatives. Histologically, cholesterol crystal aggregates and small cholesterol stones are typically observed in bile ducts[46,48].

Neonatal sclerosing cholangitis

Neonatal sclerosing cholangitis (NSC) is a rare and severe genetic cholangiopathy, commonly progressing to liver failure. The disease usually manifests in the first weeks of life. Clinical features include jaundice, hepatosplenomegaly, pale stools, coagulopathy, signs of gastrointestinal bleeding, and high serum GGT levels. Percutaneous cholangiography typically reveals an intrahepatic sclerosing cholangiopathy[49,50].

Mutations in the doublecortin domain-containing 2 (*DCDC2*) gene have been recently associated with NSC induction. *DCDC2* encodes doublecortin domain-containing protein 2 (the DCDC2 protein), which binds tubulin and facilitates microtubule polymerisation. Histologically, DCDC2 defects are generally

Table 3 Ductal plate malformation – genes and encoded proteins

Disorder	Gene	Product
ARPKD	*PKHD*	Fibrocystin/polyductin
ADPKD	*PKD1*	Polycystin 1
	PKD2	Polycystin 2
	GANAB/PKD3	Glucosidase II alpha subunit
PCLD	*PRKCSH*	Glucosidase II beta subunit
	ALG8	Alpha-1,3-glucosyltransferase
	SEC61B	SEC61 translocon subunit beta
	SEC63	Translocon component in the endoplasmic reticulum
	LRP5	LDL receptor-related protein 5
CHF-SC	*ZFYVE19*	Zinc finger FYVE-type containing 19

ARPKD: Autosomal recessive polycystic kidney disease; ADPKD: Autosomal dominant polycystic kidney disease; PCLD: Polycystic liver disease (without kidney); CHF-SC: Congenital hepatic fibrosis and sclerosing cholangiopathy.

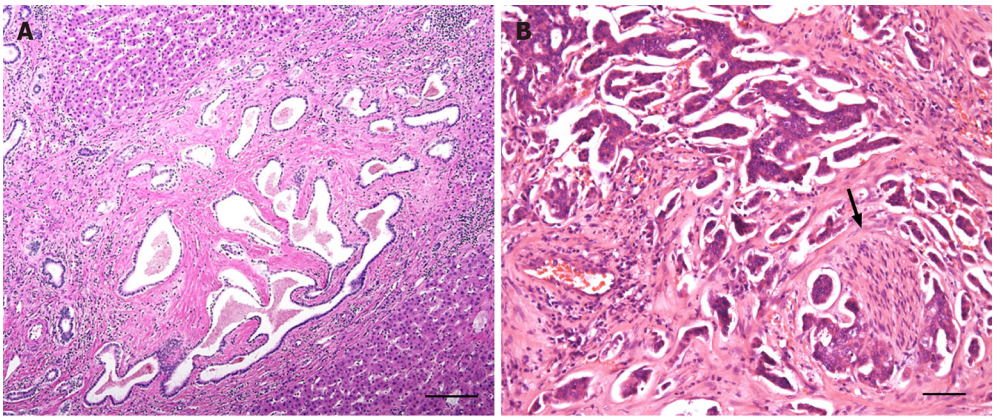

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Figure 7 Tumour-forming biliary processes. A: Hamartomatous proliferation of ductular structures in ductal plate malformation. B: Intrahepatic cholangiocarcinoma with perineural invasion (arrow). Haematoxylin and eosin; bar corresponds to 100 μm (A) and 50 μm (B).

expressed in the form of small-duct cholangiopathies, featuring focal concentric periductal lamellar fibrosis and progressive destruction of the small bile ducts[51,52]. Immunohistochemical examination typically confirms the absence of both the DCDC2 protein and the primary ciliary protein ACALT (acetylated alpha-tubulin), especially in septal and perihilar bile ducts, along with focal irregular expression in small interlobular bile ducts. Simple liver cysts have also been observed in some patients with DCDC2 deficiency[51,52].

DRUG- AND TOXIN-INDUCED CHOLANGIOPATHY

Drug-induced liver injury (DILI) encompasses a wide variety of acute and chronic forms of hepatobiliary injury that can mimic virtually any liver disease, including primary biliary conditions such as PBC or PSC. Bile duct loss, ductopenia, and biliary-type fibrosis/cirrhosis are well-documented consequences of exposure to various drugs, remedies, and toxins[53-55].

In general, drug-induced injury can be dose-dependent (intrinsic) or dose-independent (idiosyncratic). Some drugs and remedies selectively damage larger bile ducts, predominantly by dose-dependent mechanisms, and can induce biliary abnormalities with cholangiographic and histomorphological features of sclerosing cholangiopathy[49]. In most cases, however, drug-induced mechanisms are dose-independent, unpredictable, and affect cholangiocytes of small bile ducts[53].

Drug-induced cholangiopathy usually manifests in fatigue, upper abdominal pain, and features of clinical and biochemical cholestasis. Histopathological findings depend on the severity and stage of

disease progression. Mixed portal-based inflammation with eosinophils, inflammatory bile-duct injury, and centrilobular hepatocanalicular bilirubinostasis are the most common features reported in the acute phase. The chronic stage is characterised by degenerative changes of cholangiocytes, prominent bile duct injury and loss, as well as acute and chronic cholestasis (cholate stasis). Periportal ductular proliferation, associated with fibrous portal tract expansion and relatively mild portal inflammation, also occurs. Small bile duct injury can eventually progress to drug-induced ductopenia. In addition, drug-induced portal and periductal granulomata are not uncommon[53-55].

The most common drugs implicated in bile duct injury are neuroleptics, tricyclic antidepressants, anticonvulsants, antibiotics, and non-steroidal anti-inflammatory drugs. Recently, significant bile duct pathology was observed in patients treated with immune checkpoint inhibitors (CPI). Non-infective cholangitis with predominant neutrophilic or lymphocytic infiltrates, PBC-like changes, and fibrosing cholangitis mimicking sdPSC are the most common patterns of CPI-related cholangiopathy, which responds poorly to immunosuppression and can eventually lead to bile duct loss[56,57].

Diagnosis of DILI requires clinical suspicion, knowledge of the clinicopathological patterns of injury associated with the suspected agent, and exclusion of other possible causes. Underlying genetic defects and predispositions to adverse drug reactions should also be considered in certain cases.

ISCHAEMIC CHOLANGIOPATHY

Supplied by branches of the hepatic artery, the rich peribiliary vascular plexus is vulnerable to any disruption in arterial flow. Ischaemic cholangiopathy, a form of secondary sclerosing cholangiopathy (SSC), is a well-documented complication of transcatheter arterial chemoembolisation (TACE), intra-arterial infusion of chemotherapeutic agents, irradiation, radiofrequency ablation of hepatocellular carcinoma, arterial spasm after cocaine use, sickle cell crisis, HELLP syndrome, and hepatic artery thrombosis after liver transplantation[58,59]. Ischaemic cholangiopathy is characterised by injury to cholangiocytes, cytoplasmic vacuolisation, pyknotic nuclei, and subsequent desquamation of the biliary epithelial lining. Advanced lesions can lead to necrosis of the biliary tree resulting in bile leak, multiple fibrous strictures of the extrahepatic and intrahepatic bile ducts, cholangiectasis, and progressive bile duct loss. Bacterial and fungal infections are common complications[59].

Secondary sclerosing cholangitis in critically ill patients

Ischaemia of the intrahepatic bile ducts is likely involved in secondary sclerosing cholangitis in critically ill patients (SSC-CIP), a newly recognised form of SSC observed in patients after long-term treatment in intensive care units[60,61]. In addition to ischaemia, infections and toxic bile compounds are understood to contribute to the development of SSC-CIP. Interestingly, a cholangiopathy associated with some features of SSC-CIP was documented in patients with critical coronavirus disease 2019 (COVID-19) (see below).

The most frequent symptoms of SSC-CIP typically persist after recovery from the primary illness. These include jaundice, pruritus, and abdominal discomfort localised in the right upper quadrant of the abdomen. Recurrent biliary infections are also commonly observed. SSC-CIP is associated with rapid progression to liver cirrhosis[60,61,62].

Endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography (MRCP) are considered the gold standards for diagnosing SSC-CIP. Characteristic initial findings are multiple ribbon-like intraductal filling defects (biliary casts). In later stages, multiple irregular strictures, dilatations, thickening of the bile duct walls, and destruction of the intrahepatic bile ducts (except for the common bile duct, which results in a ‘pruned tree’ appearance) are routinely observed. Intrahepatic bile ducts are affected in all SSC-CIP patients, with abnormalities of the extrahepatic biliary tree occurring only in a minority of individuals[60,61].

Histopathological changes in SSC-CIP patients include degenerative epithelial alterations to the interlobular bile ducts, mild-to-moderate periductal inflammatory infiltrate, portal oedema, and periportal ductular reactions. Portal changes are accompanied by parenchymal hepatocanalicular bilirubinostasis, bile infarcts, and features of cholate stasis. Fibrous expansion of portal areas and rapid progression to advanced portoseptal fibrosis/cirrhosis have also been reported[61,62].

INFECTIOUS CHOLANGIOPATHY

A variety of microbial agents can directly impact the hepatobiliary system in both normal and immunocompromised hosts. Bacterial and viral infections are understood to play an important role in the progression of ischaemic and immune-mediated bile duct injury such as GVHD and hepatic allograft rejection. Cytomegalovirus (CMV) and hepatitis C virus (HCV) infections after interferon/ribavirin treatment have been shown to trigger ductopenic rejection after orthotopic liver transplantation[63]. Hepatitis-associated bile duct lesions featuring prominent swelling and vacuolisation of cholangiocytes

alongside periductal lymphocytic aggregates have been observed in association with HCV and hepatitis E virus infections. These lesions are mostly reversible and typically occupy individual segments along the circumferences of small bile ducts[64,65]. CMV infection of biliary epithelial cells in the presence of typical viral inclusions is not an uncommon finding in immunocompromised adults and neonates with CMV hepatitis[66].

Human immunodeficiency virus-associated cholangiopathy

Human immunodeficiency virus (HIV)-associated cholangiopathy is a biliary obstruction caused by a benign stricture of the biliary system in patients with advanced acquired immune deficiency syndrome (AIDS)[67,68]. Although the aetiology of this disease remains unclear, it is understood to occur in association with various opportunistic infections, such as CMV, *Cryptosporidium* spp., and *Giardia lamblia*. In most patients, MRCP usually results in an accurate diagnosis of HIV-associated cholangiopathy based on identification of characteristic ductal abnormalities (multiple intrahepatic and/or extrahepatic biliary strictures, papillary stenosis). Liver biopsy and histomorphological examination are reserved for inconclusive and complicated cases[68].

Post-COVID-19 cholangiopathy

Recently, a syndrome of progressive bile duct injury characterised by a marked elevation in serum ALP was reported in some patients recovering from severe COVID-19[69,70]. Although the pathogenesis of post-Covid-19 cholangiopathy has not been fully elucidated, it is likely that some of its pathogenic mechanisms resemble those observed in SSC-CIP. A combination of ischaemic cholangiopathy related to microvascular coagulopathy and an imbalance between the deleterious effects of bile components and biliary protective mechanisms likely contribute to bile duct injury. In addition, direct virus-mediated alteration of the biliary epithelium may also be involved in the pathogenesis of cholangiopathy[70,71].

The most common MRCP findings are intrahepatic and extrahepatic bile duct beading with multiple short segmental strictures and intervening dilatations together with bile duct wall thickening and hyper-enhancement, all of which are consistent with SSC. Histology typically reveals fibro-oedematous expansion of portal tracts, prominent ductular reaction, neutrophilic inflammation, and severe parenchymal cholestasis[70,71].

NEOPLASTIC CHOLANGIOPATHY

Biliary system is affected by a variety of tumour-forming and neoplastic processes, both benign and malignant.

Von Meyenburg complex is a common hamartomatous tumour-like lesion likely representing a form of ductal plate malformation (Figure 7A). Biliary hamartomas are typically found adjacent to a portal area and may be multiple[72,73].

Bile duct adenoma (BDA) is a benign lesion composed of proliferating small bile ducts. The origin of BDA is controversial and a reactive process, a hamartomatous origin and a neoplastic aetiology are considered[73].

Precursor neoplastic lesions of the biliary tract

Many cases of cholangiocarcinoma have been reported to develop through multistep carcinogenesis. The current World Health Organization classification of tumours proposes several precursor lesions of the biliary tract that may precede invasive malignancy[74,75].

Dysplastic epithelial changes can take the form of microscopic, non-invasive lesions occurring in the extrahepatic and intrahepatic bile ducts and gallbladder. This condition is known as biliary intraepithelial neoplasia (BilIN). Based on the extent of cytoarchitectural atypia, BilIN can be subdivided into low-grade (former BilIN-1 and BilIN-2) and high-grade dysplasia (former BilIN-3)[74,75].

Intraductal papillary neoplasm of the bile duct (IPNB) is a macroscopic premalignant neoplastic process with multifocal intraductal papillary or villous projections covered by a single- to multi-layered biliary-type epithelium. While the epithelial lining is usually columnar, it can also exhibit pancreaticobiliary, gastric, intestinal, or oncocytic differentiation along with varying degrees of dysplasia. Resection is the standard therapy for IPNB. However, the multifocal nature of these tumours makes complete resection difficult; therefore, tumour recurrence is a frequent complication. Tubular and mucinous forms of invasive adenocarcinoma are associated with IPNB[75,76,77].

Mucinous cystic neoplasm (MCN) is a rare lesion occurring almost exclusively in women. These tumours are typically multilocular, with cystic spaces lined by the columnar mucinous epithelium overlying ovarian-like stroma. Based on the degree of dysplasia, MCN can be subdivided into low-grade and high-grade categories. This type of lesion can also progress to invasive adenocarcinoma[75,76,78].

Intrahepatic cholangiocarcinoma

Cholangiocarcinoma (CC) is a malignant epithelial neoplasm with biliary differentiation. CC may originate from intrahepatic bile ducts (intrahepatic or peripheral CC), the confluence of the right and left hepatic ducts (hilar CC or Klatskin tumour), or distal extrahepatic bile ducts (extrahepatic distal CC). Although these subtypes differ in overall clinical outcome, they share the basic histomorphological features (Figure 7B)[75,79].

Intrahepatic CC is the second most common primary hepatic malignancy and accounts for 10%-15% primary liver cancers. Incidence is highest in south-east Asia (> 80 cases/100000 persons per year in Thailand) but lowest in Europe (0.2-1.8 cases/100000 per year)[80].

Intrahepatic CC has two main subtypes: large duct CC, originating from the larger intrahepatic bile ducts near the hepatic hilus, and small duct CC, which preferentially occurs in the periphery of the liver parenchyma[75,79].

Aetiology in most cases of CC is unknown. However, several risk factors with a high geographic prevalence have been established. Large duct CC typically originates against a background of liver fluke infection, PSC, hepaticolithiasis, biliary tract malformations, and other rare conditions, mostly associated with chronic inflammation of the biliary tract. On the other hand, the risk factors for small duct intrahepatic CC are similar to those for primary hepatocellular carcinomas, including chronic viral hepatitis and/or non-biliary fibrosis and cirrhosis[80,81].

Recent research on intrahepatic CC has identified many molecular alterations, including KRAS, TP53, ARID1A, IDH1/2, BAP1, BRAF, and other mutations[75].

Both types of intrahepatic CC are aggressive carcinomas with high mortality and poor survival rates. Resectability of the tumour indicates better prognosis, but most patients present with unresectable tumours. Adjuvant therapy, usually a combination of gemcitabine and cisplatin, is recommended for patients with node-positive disease and positive resection margins. Other therapies such as radiation, TACE and ablation have been successful to varying degrees in unresectable cases. Furthermore, a combination of targeted therapy and immunotherapy has shown promise in the treatment of patients with CC[82,83].

CONCLUSION

The small intrahepatic bile ducts are affected by a wide range of non-neoplastic and neoplastic conditions and vary considerably in clinical and morphological presentation. Given their progressive nature and limited curative options, biliary diseases account for significant morbidity and mortality in both the adult and paediatric populations. Cholangiopathies often result in end-stage liver disease requiring liver transplantation.

Although the majority of cholangiopathies are long established, recent entities such as SSC-CIP and CPI-induced cholangiopathy have complicated the application of new therapeutic agents and approaches[56,60,61]. Cholangiopathy has also developed in some critically ill patients infected by β-coronavirus severe acute respiratory syndrome coronavirus 2, isolated for the first time in Wuhan in December 2019[69,71].

Although the pathogenesis of most cholangiopathies is complex and poorly understood, environmental and genetic factors are likely to be involved. Moreover, given that each cholangiopathy has a heterogeneous pathogenesis and a variable natural history, individual responses to therapy will be different[61,71].

Early identification of the pathological mechanisms that compromise cholangiocytes and the small bile ducts is crucial in determining appropriate treatment. While large bile duct pathology is usually visualised by imaging methods, liver biopsy is still considered an effective tool in the diagnosis of small bile duct injury. However, discrepancies between histomorphological, clinical, and biochemical presentations of small bile duct disorders can hinder the diagnostic process. Clinically clear cholestatic conditions manifesting in pruritus and elevated serum ALP, GGT, cholesterol and bile salts can progress without significant bilirubinostasis on biopsy. In addition, pathognomonic morphological signs of small duct cholangiopathies are often focal and may be easily overlooked during percutaneous liver biopsy. On the other hand, early-stage cholangiopathy with a fully developed histomorphological pattern may be accompanied by only minimal and non-specific biochemical abnormalities.

Uneven fibrosis progression within the liver parenchyma is another factor that complicates the diagnostic process, notably when staging fibrosis in a chronic biliary disease. The application of standard semiquantitative scoring systems can serve to underestimate or overestimate the fibrosis stage, particularly in a limited tissue specimen. The clinician should consider not only the data obtained from the liver biopsy but also the results of imaging and other methods (FibroScan, elastography) relevant to the assessment of liver fibrosis.

The implementation of new, predominantly non-invasive diagnostic tools and methods that bridge the shortcomings of liver biopsy is needed. Moreover, further studies are required to elucidate the environmental, genetic, and epigenetic background of the processes affecting the biliary tree and to improve the clinical management of both hereditary and acquired small duct cholangiopathies.

Understanding the underlying pathogenetic mechanisms, familiarity with basic morphological patterns, and the ability to correlate microscopical findings with clinical and laboratory results are important elements when forming an overall clinical picture and selecting the optimal therapeutic approach in patients with biliary diseases. To that end, the close cooperation of all medical specialists participating in the diagnostic process is recommended.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Inferior outcomes of liver transplantation for hepatocellular carcinoma during early-COVID-19 pandemic in the United States

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Abstract

BACKGROUND

Early in the coronavirus disease 2019 (COVID-19) pandemic, there was a significant impact on routine medical care in the United States, including in fields of transplantation and oncology.

AIM

To analyze the impact and outcomes of early COVID-19 pandemic on liver transplantation (LT) for hepatocellular carcinoma (HCC) in the United States.

METHODS

WHO declared COVID-19 as a pandemic on March 11, 2020. We retrospectively analyzed data from the United Network for Organ Sharing (UNOS) database regarding adult LT with confirmed HCC on explant in 2019 and 2020. We defined pre-COVID period from March 11 to September 11, 2019, and early-COVID period as from March 11 to September 11, 2020.

RESULTS

Overall, 23.5% fewer LT for HCC were performed during the COVID period (518 *vs* 675, $P < 0.05$). This decrease was most pronounced in the months of March-April 2020 with a rebound in numbers seen from May-July 2020. Among LT recipients for HCC, concurrent diagnosis of non-alcoholic steatohepatitis significantly increased (23 *vs* 16%) and alcoholic liver disease (ALD) significantly decreased (18 *vs* 22%) during the COVID period. Recipient age, gender, BMI, and MELD score were statistically similar between two groups, while waiting list time decreased during the COVID period (279 days *vs* 300 days, $P = 0.041$). Among

pathological characteristics of HCC, vascular invasion was more prominent during COVID period (P < 0.01), while other features were the same. While the donor age and other characteristics remained same, the distance between donor and recipient hospitals was significantly increased (P < 0.01) and donor risk index was significantly higher (1.68 *vs* 1.59, P < 0.01) during COVID period. Among outcomes, 90-day overall and graft survival were the same, but 180-day overall and graft were significantly inferior during COVID period (94.7 *vs* 97.0%, P = 0.048). On multivariable Cox-hazard regression analysis, COVID period emerged as a significant risk factor of post-transplant mortality (Hazard ratio 1.85; 95%CI: 1.28-2.68, P = 0.001).

CONCLUSION
During COVID period, there was a significant decrease in LTs performed for HCC. While early postoperative outcomes of LT for HCC were same, the overall and graft survival of LTs for HCC after 180 days were significantly inferior.

Key Words: Liver transplantation; Hepatocellular carcinoma; COVID-19; Mortality; Graft failure; United Network for Organ Sharing database

Core Tip: Overall, 23.5% fewer liver transplants for hepatocellular carcinoma were performed during the coronavirus disease 2019 (COVID-19) early pandemic. Among liver transplant recipients for hepatocellular carcinoma, concurrent diagnosis of non-alcoholic steatohepatitis significantly increased. Liver transplant outcomes for hepatocellular carcinoma was worse during the early COVID-19 pandemic.

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INTRODUCTION

Since December 2019, after an initial cluster of cases of pneumonia was reported in Wuhan, China, the global spread of coronavirus disease 2019 (COVID-19) was swift, and the World Health Organization (WHO) declared it as a pandemic on March 11, 2020. This pandemic significantly impacted healthcare in the United States including transplantation[1,2] and cancer care[3], especially early in the pandemic when there were challenges in access to routine healthcare[4]. While the number of alcoholic liver disease (ALD) including alcoholic hepatitis increased during the pandemic, liver transplantation (LT) for hepatocellular carcinoma (HCC) were postponed due to the lower severity of the underlying liver disease[5]. The aim of this study was to analyze the impact of COVID-19 pandemic on LT for HCC in the United States.

MATERIALS AND METHODS

Patients and selection criteria

We evaluated all patient 18 years of age and older undergoing LT who were confirmed as HCC on pathology in the United States. Since WHO declared COVID-19 as a pandemic on March 11, 2020, we defined pre-COVID period as March 11 to September 11, 2019, and COVID period as March 11 to September 11, 2020. Patients who received re-transplant during the study were excluded. All study methods were approved by New York Medical College Institutional Review Board.

Patient characteristics and outcome variables

All data were collected from the United Network for Organ Sharing (UNOS) registry. Demographic data included diagnosis, age, gender and race. Evaluable recipient factors included body mass index (BMI), underlying etiology for liver disease, pre-transplant diabetes mellitus (DM) status, alpha-fetoprotein (AFP) level, presence of portal vein thrombosis (PVT), and model for end-stage liver disease (MELD) score at transplant. Milan criteria and UCSF criteria were created based on the pathological

findings[6,7]. HCC related factors included tumor size, number, presence of vascular invasion, and histological grade. High risk features of HCC were defined if one or more of the followings were present: More than 3 tumors, largest tumor > 5.0 cm, presence of vascular invasion, presence of metastases, and poorly differentiated[8]. Donor related factors included donor causes of death, BMI, hepatitis C virus (HCV) sero-status, cold ischemia time, distance between donor and recipient hospitals, and donor risk index[9].

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, United States) and R studio version 4.1.1 (R Studio, Inc., Boston, MA, United States). Non-parametric analysis was used to compare continuous variables between groups (Mann-Whitney *U* test 2 groups and for categorical data with the χ^2 test or Fisher's exact test for categorical data). The overall and graft survival were calculated from the date of transplant to the date of event using the Kaplan-Meier Method. The log-rank test was used to compare survival curves. Cox regression analysis was applied to assess the association of multiple covariate factors with survival between two groups. Results were presented as hazard ratios (HR) and reported with 95% confidence intervals (CI) and two-sided *P* values. For all statistical analyses, $P < 0.05$ was taken as statistically significant.

RESULTS

Recipient characteristics

During the study period, a total of 8384 individuals received LT, of which 1193 were confirmed as HCC on explant pathology. Of these patients, 675 underwent transplantation during the pre-COVID period and 518 underwent transplantation during the COVID period (Table 1). While there was a 4% reduction in all-cause LT during the COVID period, the reduction of LT for HCC was 23.5%. This decrease was most pronounced in months of March-April 2020 with a rebound in numbers seen from May-July 2020. Compared to pre-COVID period, the concurrent underlying primary etiology of liver disease among LT recipients for HCC showed a significant increase in non-alcoholic steatohepatitis (NASH) (23% *vs* 16%) and significant decrease in ALD (18% *vs* 22%) during the COVID period. The median waiting list time among patients who underwent LT, decreased during the COVID period (279 days *vs* 300 days, $P = 0.041$). There were no significant differences in the rates of pre-transplant diabetes, AFP levels, and MELD score at transplant between the two periods (Table 1).

Donor characteristics

The donor age (COVID 45 years-old *vs* pre-COVID 44 years-old, $P = 0.027$) and BMI (27.8 kg/m^2 *vs* 27.0 kg/m^2, $P < 0.001$) were significantly higher during the COVID period (Table 1). Although the distance between donor and recipient hospitals significantly increased during COVID period (88 miles *vs* 50 miles, $P < 0.001$), cold ischemia time was not significantly affected (5.87 hours *vs* 5.78 h, $P = 0.84$). The donor risk index was significantly higher during the COVID period (1.68 *vs* 1.59, $P < 0.01$) (Table 1).

Tumor characteristics

During the COVID period, the overall number of tumors with equal or greater than one high-risk features was the same (Table 2). However, there was a significantly higher rate of vascular invasion during the COVID period compared to pre-COVID period (16% *vs* 11%, $P = 0.016$). There were no significant differences in histological grade, outside of Milan criteria, and outside of UCSF criteria during the both periods.

Outcomes

Median follow-up period was 705 days in COVID period and 1059 days in pre-COVID period. Two-year overall survival (COVID period 86.5% *vs* pre-COVID 91.7%, $P = 0.0063$) and graft survival (COVID period 84.5% *vs* pre-COVID 89.6%, $P = 0.014$) were significantly inferior during the COVID period (Figure 1) (Table 3). The 180-day overall survival (COVID period 94.7% *vs* pre-COVID 97.0%, $P = 0.048$) and graft survival (COVID period 92.8% *vs* pre-COVID 95.7%, $P = 0.035$) were inferior during the COVID period. The 90-day overall survival (COVID period 97.7% *vs* pre-COVID 97.9%, $P = 0.95$) and graft survival (COVID period 96.1% *vs* pre-COVID 96.7%, $P = 0.71$) were comparable between the two periods. The risk of acute rejection after transplant before discharge was the same between pre-COVID and COVID period (17 *vs* 11, $P = 0.061$) and incidence of treatment of rejection within 6 months and 1 year were same.

Cox regression analysis was performed for overall survival and graft survival (Supplementary-Table 1 and 2). On multivariable analysis (Table 4), COVID period (HR, 1.85; 95%CI: 1.28-2.68, $P = 0.001$), recipient diabetes (HR 1.47; 95%CI: 1.04-2.06, $P = 0.027$), MELD score at transplant (HR, 1.04; 95%CI: 1.01-1.07, $P = 0.016$) significantly impacted recipient overall survival. On pathology, intrahepatic metastasis (HR 2.03; 95%CI: 1.20-3.42, $P = 0.008$) and poorly differentiated cancer (HR 2.76; 95%CI: 1.48-

Table 1 Characteristics of the study population, *n* (%)

Variable	COVID, *n* = 518	Pre-COVID, *n* = 675	*P* value
Recipient			
Age, yr, median (IQR)	64.0 (60.0, 67.8)	63.0 (59.0, 67.0)	0.2
Male	405 (78)	529 (78)	0.98
Race, White	328 (63)	388 (57)	0.12
African American	36 (6.9)	47 (7.0)	
Hispanic	108 (21)	153 (23)	
Asian	39 (7.5)	69 (10)	
Others	7 (1.4)	19 (2.8)	
BMI median (IQR) kg/m^2	29.3 (25.7, 33.2)	28.9 (25.3, 33.0)	0.26
Etiology, HCV	180 (35)	258 (38)	0.034
HBV	33 (6.4)	43 (6.4)	
ALD	95 (18)	149 (22)	
NASH	118 (23)	107 (16)	
Others	92 (18)	118 (17)	
Blood Type, A	203 (39)	235 (35)	0.13
AB	18 (3.5)	27 (4.0)	
B	76 (15)	82 (12)	
O	221 (43)	331 (49)	
Diabetes	208 (40)	255 (38)	0.4
HCV positive serostatus	229 (46)	319 (49)	0.28
Previous abdominal surgery	229 (45)	330 (49)	0.19
Portal vein thrombosis	66 (13)	106 (16)	0.19
Hemodialysis at transplant	8 (1.6)	8 (1.2)	0.59
TIPSS	30 (5.8)	32 (4.7)	0.42
AFP ng/mL, median (IQR)	6.0 (3.0, 15.0)	7.0 (4.0, 16.0)	0.21
MELD score, median (IQR)	10 (8, 14)	10 (8, 14)	0.33
MELD exception	510 (98)	658 (97)	0.24
Mechanical ventilation	0 (0)	2 (0.3)	0.51
Waiting days, median (IQR)	279 (221, 392)	300 (228, 424)	0.041
Patient location at transplant			0.62
ICU at time of transplant	2 (0.4)	5 (0.7)	
Non-ICU inpatient at time of transplant	19 (3.7)	31 (4.6)	
Outpatient	487 (96)	639 (95)	
Donor			
Age, yr, median (IQR)	45.0 (32.0, 59.0)	44.0 (30.0, 56.0)	0.027
Male	326 (63)	421 (62)	0.84
Race, White	322 (62)	428 (63)	0.058
African American	104 (20)	117 (17)	
Hispanic	73 (14)	92 (14)	
Asian	15 (2.9)	17 (2.5)	
Others	4 (0.8)	21 (3.1)	

BMI median (IQR) kg/m^2	27.8 (24.4, 33.2)	27.0 (23.8, 30.9)	< 0.001
Blood Type, A	204 (39)	237 (35)	0.12
AB	14 (2.7)	16 (2.4)	
B	80 (15)	88 (13)	
O	220 (42)	334 (49)	
HCV NAT positive	37 (7.1)	39 (5.8)	0.34
HCV antibody positive	59 (11)	76 (11)	0.94
Donor causes of death: Anoxia	234 (45)	265 (39)	0.026
Cerebrovascular accident	158 (31)	221 (33)	
Head trauma	104 (20)	172 (25)	
Central nervous system tumor	2 (0.4)	4 (0.6)	
Others	20 (3.9)	13 (1.9)	
Donor after cardiac death	62 (12)	80 (12)	0.95
Organ Share, Local	241 (47)	508 (75)	< 0.001
Regional	174 (34)	145 (21)	
National	103 (20)	22 (3.3)	
Donor risk index, median (IQR)	1.68 (1.45, 2.06)	1.59 (1.35, 1.91)	< 0.001

COVID: Coronavirus disease; IQR: Interquartile range; BMI: Body mass index; HCV: Hepatitis C virus; HBV: Hepatitis B virus; ALD: Alcoholic liver disease; NASH: Non-alcoholic steatohepatitis; TIPSS: Transjugular intrahepatic portosystemic shunt; AFP: Alpha-fetoprotein; MELD: Model for end-stage liver disease; ICU: Intensive care units; NAT: Nucleic acid amplification test.

5.15, P = 0.001) significantly impacted recipient overall survival.

DISCUSSION

This study was undertaken to examine the effect of COVID-19 on LT for HCC in the United States using the UNOS database. During COVID period, there was a significant reduction in the number of LTs performed for HCC compared to pre-COVID period. Even with overall reduction in the number LTs performed during the same period, the decrease was much pronounced in patients with underlying HCC (4% decrease in all-cause LT *vs* 23.5% decrease in LT for HCC). In addition, both graft and patient survival after 180 days during COVID period were significantly inferior compared to pre-COVID period.

During early pandemic, the unprecedented burden of COVID-19 on healthcare system disrupted both transplantation and oncological care. Due to resource reallocation, cancer patients experienced delays in diagnosis and treatment, as well as treatment interruptions including surgery and chemotherapy[3,4]. HCC is an aggressive form of liver cancer which requires a prompt, multimodal approach for diagnosis and management. Similar to outpatient management of other cancers, challenges in care of HCC were prompted by overall disruption of healthcare during COVID-19[10,11]. Despite efforts to optimize care, there was an overall reduction in HCC surveillance and subsequent treatment during the early COVID pandemic[12-14]. Because of the unknown risk-benefit of proceeding with liver transplantation and introducing iatrogenic immune-suppression, liver transplantation was limited to patients who had higher risk of imminent death while on the waitlist[1,2]. Since LT candidates for HCC often had lower MELD scores, this likely contributed to the disproportional decrease in LT for HCC during early COVID period.

The current leading indication for liver transplant in the United States is ALD[15]. During the COVID pandemic, there was a significant increase in alcohol misuse, which resulted higher rates of hospitalization from ALD, progression to fulminant liver disease and LT for acute and chronic ALD[16,17]. However, when looking at the underlying primary etiology of HCC for patients who received LT for HCC, the number and ratio of ALD significantly decreased during the COVID, while the number and ratio of NASH significantly increased. Though further studies are needed to investigate the cause of this seemingly contradictory finding, one possible explanation is increased alcohol recidivism in HCC patients with ALD as the primary underlying etiology, which could disqualify them as LT candidates in most transplant centers.

Table 2 Pathological characteristics of hepatocellular carcinoma in liver transplant, *n* (%)

Variable	COVID, *n* = 518	Pre-COVID, *n* = 675	*P* value
Number of tumors			
1	229 (44)	333 (49)	
2	116 (22)	146 (22)	
3	80 (15)	77 (11)	
4	36 (6.9)	47 (7.0)	
5	22 (4.2)	33 (4.9)	
6	31 (6.0)	38 (5.6)	
Tumor numbers > 3	89 (17)	118 (17)	0.89
Outside UCSF criteria	131 (25)	178 (26)	0.71
Outside Milan criteria	203 (39)	262 (39)	0.84
Tumor max size, cm median (IQR)	2.80 (1.80, 4.00)	2.90 (1.90, 4.00)	0.92
Worst tumor histology			
Complete tumor necrosis	132 (25)	185 (27)	0.5
Moderate differentiated	265 (51)	344 (51)	
Poorly differentiated	26 (5.0)	41 (6.1)	
Well differentiated	95 (18)	105 (16)	
Vascular invasion	6 (1.2)	11 (1.6)	0.019
Macro			
Micro	77 (15)	65 (9.6)	
None	435 (84)	599 (89)	
Lymph node involvement	8 (1.5)	4 (0.6)	0.1
Extra hepatic spread	7 (1.4)	6 (0.9)	0.76
Intrahepatic metastasis	42 (8.1)	36 (5.3)	0.066
Previous treatment for HCC	511 (99)	657 (97)	0.21
High risk features	174 (34)	198 (29)	0.12

COVID: Coronavirus disease; IQR: Interquartile range; UCSF: University of California San Francisco; HCC: Hepatocellular carcinoma.

Table 3 Outcomes of liver transplant for hepatocellular carcinoma, *n* (%)

Variable		COVID, *n* = 518	Pre COVID, *n* = 675	*P* value
Month	March	68 (13)	132 (20)	0.008
	April	86 (17)	123 (18)	
	May	108 (21)	97 (14)	
	June	78 (15)	95 (14)	
	July	84 (16)	99 (15)	
	August	94 (18)	129 (19)	
Distance from donor hospital, miles, median (IQR)		88 (23, 188)	50 (8, 164)	< 0.001
Cold ischemia time, hours median (IQR)		5.87 (4.71, 7.07)	5.78 (4.65, 7.12)	0.84
Acute rejection before discharge		17 (3.3)	11(1.6)	0.061
Treatment rejection within 6 month		27 (6.4)	38 (6.6)	0.88

Treatment rejection within 1 year	35 (8.4)	45 (8.4)	0.99
Length of stay, days median (IQR)	8 (6, 11)	8 (6, 12)	0.60
Survival rate			
90-day overall survival	97.7	97.9	0.95
180-day overall survival	94.7	97.0	0.048
Two-year overall survival	86.5	91.7	0.0063
90 day graft survival	96.1	96.7	0.71
180 day graft survival	92.8	95.7	0.035
Two-year graft survival	84.5	89.6	0.014

IQR: Interquartile range; COVID: Coronavirus disease.

Table 4 Multivariable Cox regression analysis of factors affecting overall mortality

Variable	HR	95%CI	*P* value
COVID period	1.85	1.28, 2.68	0.001
Recipient age	1.02	0.99, 1.05	0.15
Recipient diabetes	1.47	1.04, 2.06	0.027
MELD score	1.04	1.01, 1.07	0.016
Donor age	1.01	1.00, 1.02	0.10
Donation after cardiac death	0.59	0.31, 1.14	0.12
Pathology			
Intrahepatic metastasis	2.03	1.20, 3.42	0.008
Lymph node invasion	2.49	0.90, 6.86	0.078
Worst tumor histology			
Complete tumor necrosis	reference	-	
Well differentiated	1.11	0.63, 1.97	0.70
Moderate differentiated	1.27	0.81, 1.99	0.30
Poorly differentiated	2.76	1.48, 5.15	0.001

HR: Hazard ratio; CI: Confidence intervals; MELD: Model for end-stage liver disease; COVID: Coronavirus disease.

Similar to the decrease in graft and patient survival seen in all-cause LT during the early COVID period[5], the cause for significant decrease in graft and patient survival after 180 days in LT for HCC is likely multifactorial. During early COVID, many centers decreased the use of immunosuppression to mitigate the risk of infection[18]. Such conservative approaches may have contributed to increased rates of acute rejection prior to discharge[5]. In our cohort, although it is not statistically significant, we observed a similar trend in increased rates of rejection prior to discharge in those who were transplanted during COVID period. During the follow up, the incidences of acute rejection were comparable between pre-COVID and COVID period.

Another potential contributing factor towards inferior graft and patient survival in LT for HCC during the COVID period is the progression of HCC at the time of LT. Although there were no significant differences in histological grade and the number of patients outside Milan/USCF criteria, there was a significantly higher rates of vascular invasion during the COVID period compared to pre-COVID period. Vascular invasion is one of the known risk factors for recurrent HCC and detection of metastasis post-LT, which is associated with high morbidity and mortality[19]. As delays in oncological care and radiological testing were prevalent during this period, any such delay may have resulted in progression of HCC which was not grossly evident prior to LT.

In February 2020, the new liver allocation policy was also implemented which allowed for broader sharing of the organs across different organ procurement organizations[20]. This likely contributed to increase in donor risk index and farther distances between donor and recipient hospitals. Long term

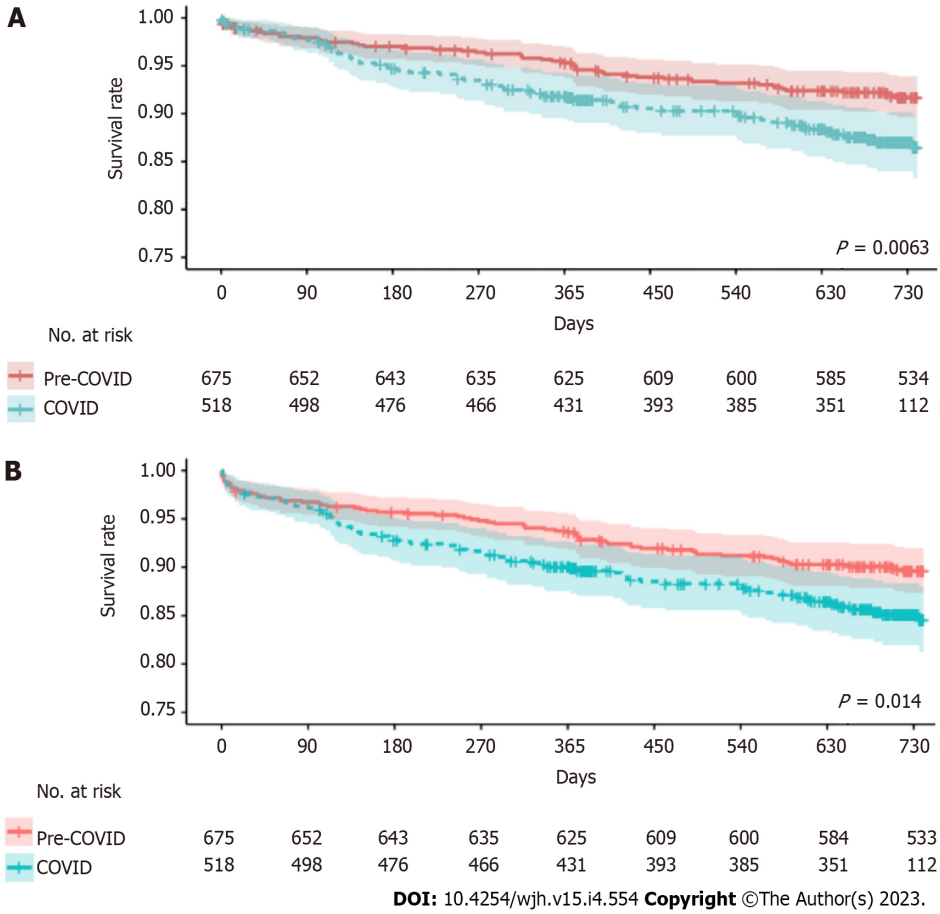

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Figure 1 Post-transplant survival curves between pre-coronavirus disease and coronavirus disease period. A: Comparison of overall survival between pre-coronavirus disease (COVID) and COVID period; B: Comparison of graft survival between pre-COVID and COVID period.

impact of these factors on the graft and overall outcomes still needs to be determined.

Limitations

This study was performed retrospectively using UNOS database. Other indirect effects of COVID-19, such as psychosocial impact, medication non-compliance, rates of recidivism of alcohol use, rates of community/household spread of COVID-19 are not available in the database and may impact the outcomes.

CONCLUSION

During the early-COVID period (from March 11, 2020 to September 11, 2020), the overall number of LT for HCC decreased and post-transplant graft and patient survival were inferior compared to pre-COVID period.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) pandemic significantly impacted healthcare in the United States including transplantation and cancer care, especially early in the pandemic when there were challenges in access to routine healthcare.

Research motivation

To analyze the impact of COVID-19 pandemic on Liver transplantation (LT) for Hepatocellular carcinoma (HCC) in the United States.

Research objectives

All patient 18 years of age and older undergoing LT who were confirmed as HCC on pathology in the United States.

Research methods

Since WHO declared COVID-19 as a pandemic on March 11, 2020, we defined pre-COVID period as March 11 to September 11, 2019, and COVID period as March 11 to September 11, 2020.

Research results

Overall, 23.5% fewer LT for HCC were performed during the COVID period (518 *vs* 675, $P < 0.05$). Among pathological characteristics of HCC, vascular invasion was more prominent during COVID period ($P < 0.01$), while other features were the same. Among outcomes, 90-day overall and graft survival were the same, but 180-day overall and graft were significantly inferior during COVID period (94.7 *vs* 97.0%, $P = 0.048$). On multivariable Cox-hazard regression analysis, COVID period emerged as a significant risk factor of post-transplant mortality (Hazard ratio 1.85; 95%CI: 1.28-2.68, $P = 0.001$).

Research conclusions

During COVID period, there was a significant decrease in LTs performed for HCC. While early postoperative outcomes of LT for HCC were same, the overall and graft survival of LTs for HCC after 180 days were significantly inferior.

Research perspectives

To analyze the effects of COVID-19 pandemic in the long-term effects for LT for HCC.

FOOTNOTES

Author contributions: Lee IS and Okumura K contributed equally to this work; Lee IS, Okumura K, and Dhand A contributed to study design; Lee IS, Okumura K, Misawa R, Nishida S and Dhand A analyzed data and writing of the manuscript; Sogawa H, Veillette G, John D and Diflo T contributed to critical revision; all authors approved the final manuscript.

Institutional review board statement: All study methods were approved by New York Medical College Institutional Review Board.

Informed consent statement: Informed consent was waived for patients in the study because of the study's retrospective nature and the use of a retrospective database.

Conflict-of-interest statement: The authors have no conflict of interest to declare.

Data sharing statement: The data that support the findings of this study are available from the corresponding author upon reasonable request. The data reported here have been supplied by the UNOS as the contractor for the OPTN. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the OPTN or the United States Government.

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ORIGINAL ARTICLE

Retrospective Study

Peptic ulcer disease in non-alcoholic fatty liver disease hospitalizations: A new challenge on the horizon in the United States

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Abstract

BACKGROUND

Peptic ulcer disease (PUD) is frequently seen in patients with liver cirrhosis. However, current literature lacks data on PUD in non-alcoholic fatty liver disease (NAFLD) hospitalizations.

AIM

To identify trends and clinical outcomes of PUD in NAFLD hospitalizations in the United States.

METHODS

The National Inpatient Sample was utilized to identify all adult (≥ 18 years old) NAFLD hospitalizations with PUD in the United States from 2009-2019. Hospitalization trends and outcomes were highlighted. Furthermore, a control group of adult PUD hospitalizations without NAFLD was also identified for a comparative analysis to assess the influence of NAFLD on PUD.

RESULTS

The total number of NAFLD hospitalizations with PUD increased from 3745 in 2009 to 3805 in 2019. We noted an increase in the mean age for the study population from 56 years in 2009 to 63 years in 2019 ($P < 0.001$). Racial differences were also prevalent as NAFLD hospitalizations with PUD increased for Whites and Hispanics, while a decline was observed for Blacks and Asians. The all-cause inpatient mortality for NAFLD hospitalizations with PUD increased from 2% in 2009 to 5% in 2019 ($P < 0.001$). However, rates of *Helicobacter pylori* (*H. pylori*) infection and upper endoscopy decreased from 5% in 2009 to 1% in 2019 ($P < 0.001$) and from 60% in 2009 to 19% in 2019 ($P < 0.001$), respectively. Interestingly, despite a significantly higher comorbidity burden, we observed lower inpatient mortality (2% *vs* 3%, $P = 0.0004$), mean length of stay (LOS) (11.6 *vs* 12.1 d, $P < 0.001$), and mean total healthcare cost (THC) ($178598 *vs* $184727, $P < 0.001$) for NAFLD hospitalizations with PUD compared to non-NAFLD PUD hospitalizations. Perforation of the gastrointestinal tract, coagulopathy, alcohol abuse, malnutrition, and fluid and electrolyte disorders were identified to be independent predictors of inpatient mortality for NAFLD hospitalizations with PUD.

CONCLUSION

Inpatient mortality for NAFLD hospitalizations with PUD increased for the study period. However, there was a significant decline in the rates of *H. pylori* infection and upper endoscopy for NAFLD hospitalizations with PUD. After a comparative analysis, NAFLD hospitalizations with PUD had lower inpatient mortality, mean LOS, and mean THC compared to the non-NAFLD cohort.

Key Words: Non-alcoholic fatty liver disease; Peptic ulcer disease; Trends; Outcomes; Mortality

Core Tip: Due to dietary and lifestyle changes, the prevalence of non-alcoholic fatty liver disease (NAFLD) is on the rise worldwide. Peptic ulcer disease (PUD) is commonly seen in patients with liver cirrhosis. However, data on PUD in NAFLD hospitalizations is currently lacking. In this study, we noted an increase in inpatient mortality for NAFLD hospitalizations with PUD in the United States. The rates of *Helicobacter pylori* infection and upper endoscopy for NAFLD hospitalizations with PUD were on the decline. Despite a higher comorbidity burden, inpatient mortality, mean length of stay, and mean total healthcare cost were lower for NAFLD hospitalizations with PUD compared to the non-NAFLD cohort.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) encompasses a wide range of conditions primarily charac-

terized by the presence of hepatic steatosis which is identified on radiological imaging or histology after other secondary causes of fat deposition have been excluded[1]. Based on histological findings, it is further subdivided into NAFL, which is hepatic steatosis without hepatocellular injury, and non-alcoholic steatohepatitis (NASH) characterized by hepatic steatosis and inflammation with hepatocyte injury. NAFLD usually progresses linearly from steatosis and hepatitis to fibrosis, cirrhosis, and ultimately hepatocellular carcinoma. Risk factors commonly implicated in the development of NAFLD include obesity, diabetes mellitus, hypertriglyceridemia, and metabolic syndrome[2]. The global prevalence of NAFLD is estimated to be 25% and is expected to rise further due to the rising incidence and prevalence of obesity worldwide[3]. In the United States, approximately 80 million people have NAFLD, with NASH being the second leading cause of liver transplant[4].

Peptic ulcer disease (PUD) involves acid-induced mucosal disruption in the upper gastrointestinal (GI) tract, usually in the stomach or proximal duodenum. *Helicobacter pylori* (*H. pylori*) infection and the excessive use of non-steroidal anti-inflammatory drugs are the leading causes of PUD[5]. Additionally, increasing age, smoking, alcohol use, and obesity have a strong association with PUD[6]. Although the prevalence of self-reported physician-diagnosed ulcer disease in the United States was as high as 10% at the end of the 20th century, there has been a decrease in prevalence and hospitalizations for PUD in the last few decades, primarily due to advancements in *H. pylori* eradication and increasing utilization of proton pump inhibitors for acid suppression[7,8].

The association between alcoholic liver disease and PUD has been well established with studies reporting a higher prevalence of PUD in patients with alcoholic liver cirrhosis[9]. Additionally, a study by Nojkov and Cappell noted that PUD was the most common cause of non-variceal hemorrhage in cirrhotics and carried a higher rate of re-bleeding, delayed ulcer healing, and recurrence when compared to the general population[10]. However, there continue to be significant knowledge gaps on PUD in NAFLD hospitalizations. Hence, we addressed the knowledge gaps in current literature as we identified hospitalization trends, outcomes, and predictors of mortality for NAFLD hospitalizations with PUD. Furthermore, we also performed a comparative analysis between NAFLD hospitalizations with PUD and non-NAFLD PUD hospitalizations to determine the influence of NALFD on PUD.

MATERIALS AND METHODS

Design and data source

The study cohort was derived from the National Inpatient Sample (NIS) database which is one of the largest, publicly available, multi-ethnic databases in the United States. The NIS, part of the Healthcare Cost and Utilization Project group of databases, consists of data on inpatient admissions submitted by hospitals across the United States to state-wide data organizations, covering 97% of the United States population[11]. It approximates a 20-percent stratified sample, and the dataset is weighted to obtain national estimates[12]. For the 2009-2019 study period, the NIS database was coded using the International Classification of Diseases (ICD)-9/10 coding systems.

Study population

We utilized the NIS to obtain all adult (≥ 18 years) NAFLD hospitalizations with PUD in the United States from 2009-2019. Furthermore, a control group of all adult PUD hospitalizations without NAFLD were identified for comparative analysis.

Statistical analysis and outcome measures

Statistical analysis was conducted using SAS 9.4 (SAS Institute Inc, Cary, NC) while accounting for the weights in the stratified survey design. The weights were considered during statistical estimation by incorporating variables for strata, clusters, and weight to discharges in the NIS. Descriptive statistics were provided, including mean (standard deviation) for continuous variables and count (percentage) for categorical variables. To test for the trend for proportions of binary variables in years, the Cochran-Armitage trend test was implemented. The trend for the averages of continuous variables in years was examined using linear regression. The Rao-Scott design-adjusted chi-square test, which takes the stratified survey design into account, examined the association between two categorical variables. All analytical results were statistically significant when the *P*-values ≤ 0.05.

Ethical considerations

The NIS database lacks any patient and hospital-specific identifiers. Hence, this study was exempt from Institutional Review Board (IRB) review as per guidelines put forth by our institutional IRB for research on database studies.

RESULTS

Hospitalization characteristics for NAFLD hospitalizations with PUD

Overall, there was no decline in the total number of NAFLD hospitalizations with PUD (3745 in 2009 to 3805 in 2019, with a peak of 6885 in 2014) (Table 1). The mean age increased from 56.0 years in 2009 to 63.0 years in 2019 ($P < 0.001$), with a significant increase noted for the 65-79 age group (26% in 2009 to 46% in 2019). A majority of NAFLD hospitalizations with PUD were for females and Whites. Racial differences were also noted as there was a declining trend of NAFLD hospitalizations with PUD for Blacks from 10% in 2009 to 5% in 2019 ($P = 0.01$) and Asians from 3% in 2009 to 2% in 2019 ($P = 0.01$), while Whites and Hispanics had a rising trend (Table 1 and Figure 1). Furthermore, rates of *H. pylori* infection and upper endoscopy decreased from 2009 to 2019 (Table 1). Most NAFLD hospitalizations with PUD were at large hospitals, and admissions in urban teaching hospitals increased from 40% in 2009 to 80% in 2019 ($P < 0.001$). Overall, Medicare was the largest insurer for NAFLD hospitalizations with PUD.

Outcomes for NAFLD hospitalizations with PUD

We noted a rising trend of all-cause inpatient mortality for NAFLD hospitalizations with PUD from 2% in 2009 to 5% in 2019 ($P < 0.001$) (Table 2). However, inpatient mortality for Whites declined from 81% in 2009 to 64% in 2019 ($P = 0.04$) within the race analysis. We did not find a statistically significant trend for mean length of stay (LOS) and mean total healthcare cost (THC). Furthermore, the rates of GI tract perforation decreased [33% (2009) to 8% (2019), $P = 0.02$] but the proportion of patients with GI bleeding increased [0% (2009) to 11% (2019), $P = 0.04$].

Comparative analysis of NAFLD and non-NAFLD hospitalizations with PUD

NAFLD hospitalizations with PUD were younger (58.6 *vs* 65.3 years, $P < 0.001$), and had more Whites and Hispanics compared to the non-NAFLD subgroup (Table 3). A Charlson Comorbidity Index (CCI) ≥ 3 was noted in a higher proportion of NAFLD hospitalizations with PUD (55%) compared to non-NAFLD PUD hospitalizations (49%) ($P < 0.001$). Although NAFLD hospitalizations with PUD had a higher proportion of patients that underwent upper endoscopy (49% *vs* 41%, $P < 0.001$), the rates of *H. pylori* infection was not statistically different between the cohorts (Table 3).

Despite a higher CCI score, the all-cause inpatient mortality was lower (2% *vs* 3%, $P = 0.0004$), for NAFLD-PUD hospitalizations compared to the non-NAFLD-PUD hospitalizations (Table 4). Furthermore, the mean LOS was shorter (11.6 *vs* 12.1 d, $P < 0.001$), the and mean THC was lower ($178598 and $184727, $P < 0.001$) for NAFLD-PUD hospitalizations compared to non-NAFLD-PUD hospitalizations (Table 4). There was no statistical difference in the proportion of patients with complications such as GI bleeding and perforation between the 2 groups.

Predictors of mortality for NAFLD hospitalizations with PUD

Significant predictors of all-cause inpatient mortality for NAFLD hospitalizations with PUD included GI tract perforation (aHR = 2.71, 95%CI: 1.37-5.35, $P = 0.004$), coagulopathy (aHR = 2.24, 95%CI: 0.74-0.84, $P < 0.001$), fluid and electrolyte disorders (aHR = 1.92, 95%CI: 1.82-2.01, $P < 0.001$), alcohol abuse (aHR = 1.51, 95%CI: 1.42-1.61, $P < 0.001$), and protein-calorie malnutrition (aHR = 1.16, 95%CI: 1.11-1.22, $P < 0.001$) (Table 5).

DISCUSSION

PUD is believed to be the most common cause of non-variceal GI bleeding in liver cirrhosis patients. However, data on PUD in NAFLD hospitalizations is lacking. Ours is the only study in current literature that evaluates the trends of hospitalization characteristics and outcomes for NAFLD hospitalizations with PUD and further compares NAFLD hospitalizations with PUD to non-NAFLD PUD hospitalizations using the NIS database. In this study, we did not find a decline in the total number of NAFLD hospitalizations with PUD. The all-cause inpatient mortality increased from 2% in 2009 to 5% in 2019 in the United States. However, the rates of upper endoscopy and *H. pylori* infection declined for NAFLD hospitalizations with PUD. Furthermore, NAFLD hospitalizations with PUD had lower mortality, LOS, and THC compared to the non-NAFLD group, despite a higher comorbidity burden. An understanding of the trends, outcomes, and influence of NAFLD on PUD is crucial as it may help gastroenterologists identify individuals at the greatest risk of adverse outcomes and complications, thereby preventing morbidity and mortality.

Recent studies have demonstrated a dramatic increase in the prevalence and hospitalization rates for patients with NAFLD, which could have led to the slightly increased number of hospitalizations noted in our study[13,14]. This is despite the fact that there has been an overall decline in hospitalization rates for PUD in the United States[15]. Furthermore, racial differences have also been noted in NAFLD hospitalizations for ethnic minorities. Per current literature, the highest and lowest rates of NAFLD

Table 1 Hospitalization trends for non-alcoholic fatty liver disease hospitalizations with peptic ulcer disease in the United States from 2009-2019

Variable	Years									
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Total hospitalizations	3745	4563	5230	5655	5759	6885	5745	2880	3070	3430
Mean age (yr)	56.01 ± 0.8	57.07 ± 0.75	56.68 ± 0.81	57.1 ± 0.14	57.1 ± 0.41	57.4 ± 0.59	57.5 ± 0.97	62.4 ± 0.41	62.8 ± 0.8	63.7 ± 0.74
Age groups, yr (%)										
18-34	9	8	8	8	7	8	8	3	4	2
35-49	25	24	25	25	23	22	21	12	11	15
50-64	39	42	41	39	42	42	39	44	40	36
65-79	26	25	26	27	28	28	32	42	44	47
≥ 80	< 1	1	1	1	< 1	< 1	< 1	1	1	1
Gender (%)										
Male	45	42	43	43	44	44	45	36	40	40
Female	55	48	57	58	56	56	55	64	60	50
Race (%)										0.01
White	72	73	70	71	72	71	70	74	76	76
Black	10	8	9	10	9	11	10	6	5	5
Hispanic	11	13	14	13	12	11	13	14	15	15
Asian	3	3	3	3	2	3	3	2	2	2
Native American	1	< 1	1	1	1	1	1	2	1	1
Other	3	3	3	3	3	4	3	3	2	4
CCI (%)										
CCI = 0	0	0	0	0	0	0	0	0	0	0
CCI = 1	34	32	34	32	32	31	31	6	6	6
CCI = 2	27	24	23	22	22	22	25	13	8	10
CCI ≥ 3	39	44	43	47	46	47	44	86	86	86
Hospital region (%)										
Northeast	13	12	14	16	15	14	14	13	13	16
Midwest	24	24	22	22	22	21	21	28	29	29
South	39	41	43	21	42	43	44	38	37	35
West	24	23	21	21	21	21	21	20	21	19
Hospital bed-size (%)										
Small	8	11	11	13	11	16	16	15	16	16
Medium	25	25	22	29	26	32	29	24	25	28
Large	67	64	67	59	63	52	55	61	59	56
Hospital location and teaching status (%)										
Rural	8	10	11	10	10	7	7	6	5	5
Urban non-teaching	47	50	45	41	37	26	27	21	20	14
Urban teaching	46	40	44	49	53	67	66	73	75	81
Primary payer										
Medicare	41	42	41	44	43	44	44	53	60	60

Medicaid	13	15	14	15	15	16	16	14	11	11
Private	36	35	35	33	34	33	33	30	25	26
Other	10	8	10	8	8	7	7	2	3	3
Median household income (%)										
1st (0-25th)	26	27	30	28	31	28	31	31	27	29
2nd (26th-50th)	25	24	25	24	26	29	24	27	32	32
3rd (51st-75th)	30	24	24	26	24	23	26	24	25	21
4th (76th-100th)	19	24	21	22	19	20	19	17	15	18
Upper endoscopy (%)	60	59	62	58	59	59	62	20	22	18

CCI: Charlson Comorbidity Index.

Table 2 Trends of outcomes for non-alcoholic fatty liver disease hospitalizations with peptic ulcer disease in the United States from 2009-2019

Outcome	Years											*P* value
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	
Inpatient mortality (%)	2	1	2	2	2	2	1	4	4	5	5	< 0.001
Gender-specific inpatient mortality (%)												0.2
Male	25	21	28	57	53	38	40	37	52	32	31	
Female	75	79	72	43	47	62	60	63	48	48	48	
Race-specific inpatient mortality (%)												0.4
White	81	53	89	48	79	73	73	71	81	61	64	
Black	7	0	0	14	0	4	0	4	4	6	11	
Hispanic	12	47	11	19	16	19	7	17	8	19	14	
Asian	0	0	0	10	5	0	0	4	0	3	6	
Native American	0	0	0	5	0	0	7	0	4	3	6	
Others	0	0	0	5	0	4	13	4	4	6	0	
Age-group specific inpatient mortality (%)												0.1
18-34	7	0	0	0	0	3	0	0	0	0	0	
35-49	13	26	16	13	0	17	14	9	22	14	6	
50-64	51	36	33	31	29	34	36	41	52	31	48	
65-79	28	24	36	56	71	41	50	50	26	48	45	
≥ 80	0	13	14	0	0	3	0	0	0	3	0	
Length of stay (d)	17.1 ± 0.59	11.8 ± 0.76	16.3 ± 0.58	9.2 ± 0.85	9.0 ± 0.01	8.2 ± 0.68	10.1 ± 0.33	9.6 ± 0.49	17.3 ± 0.33	9.2 ± 0.90	11.2 ± 0.22	0.06
Total hospital charge ($)	182296 ± 760	104265 ± 620	215085 ± 130	172837 ± 170	157079 ± 890	105031 ± 760	136876 ± 800	134573 ± 730	373045 ± 450	143284 ± 940	174044 ± 550	0.8
Complications (%)												
Bleeding	0	21	0	0	5	10	7	17	7	10	11	0.4
Perforation	33	12	35	29	16	**3**	13	17	11	3	8	0.02

Table 3 Comparative analysis of hospitalization characteristics for non-alcoholic fatty liver disease hospitalizations with peptic ulcer disease and non-NALFD hospitalizations with peptic ulcer disease in the United States from 2009-2019

	NAFLD hospitalizations with PUD	Non-NAFLD hospitalizations with PUD	*P* value
Total hospitalizations	50769 (1%)	4624628 (99%)	
Mean age (yr)	58.6 ± 0.27	65.3 ± 0. 80	< 0.001
Age group, yr (%)			< 0.001
18-34	6	6	
35-49	21	15	
50-64	40	33	
65-79	32	40	
≥ 80	1	6	
Gender (%)			< 0.001
Male	42	49	
Female	48	51	
Race (%)			< 0.001
White	72	70	
Black	9	14	
Hispanic	13	9	
Asian	3	3	
Native American	1	1	
Other	3	3	
CCI (%)			< 0.001
CCI = 0	0	0	
CCI = 1	25	30	
CCI = 2	20	22	
CCI ≥ 3	55	49	
Upper endoscopy (%)	49	41	< 0.001
H. pylori (%)	3	3	0.5
Hospital region (%)			< 0.001
Northeast	14	18	
Midwest	24	23	
South	41	39	
West	21	20	
Hospital bed size (%)			< 0.001
Small	14	16	
Medium	27	28	
Large	59	56	
Hospital location and teaching status (%)			< 0.001
Rural	8	10	
Urban nonteaching	32	34	
Urban teaching	60	56	
Expected primary payer (%)			< 0.001
Medicare	47	61	

Medicaid	14	12	
Private	32	21	
Other	7	5	
Median household income (quartile) (%)			< 0.001
1st (0-25th)	29	31	
2nd (26th-50th)	27	26	
3rd (51st-75th)	25	24	
4th (76th-100th)	20	19	

CCI: Charlson Comorbidity Index; NAFLD: Non-alcoholic fatty liver disease; PUD: Peptic ulcer disease.

Table 4 Comparative analysis of outcomes for non-alcoholic fatty liver disease hospitalizations with peptic ulcer disease and non-NAFLD hospitalizations with peptic ulcer disease in the United States from 2009-2019

Outcomes	NAFLD hospitalizations with PUD	Non-NAFLD hospitalizations with PUD	*P* value
Inpatient mortality (%)	2	3	0.0004
Gender-specific inpatient mortality (%)			< 0.001
Male	38	54	
Female	62	46	
Race-specific inpatient mortality (%)			< 0.001
White	70	72	
Black	6	12	
Hispanic	16	9	
Asian	3	4	
Native American	3	1	
Others	3	3	
Age-group specific inpatient mortality (%)			< 0.001
18-34	1	2	
35-49	13	7	
50-64	39	30	
65-79	44	49	
≥ 80	2	12	
Length of stay (d)	11.6	12.1	< 0.001
Total healthcare cost ($)	178598	184727	< 0.001
Complications (%)			
Bleeding	8	6	0.2
Perforations	14	18	0.1

NAFLD: Non-alcoholic fatty liver disease; PUD: Peptic ulcer disease.

hospitalizations are for Hispanics and African Americans, respectively[13,16]. This has been attributed to dietary habits, lifestyle, and genetics as Hispanics have an allele of the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) that favors hepatic fat storage, while African Americans possess a different allele of the same gene associated with lower hepatic fat content[17,18]. Our study echoed similar findings as we noted a rising trend of NAFLD hospitalizations with PUD for Hispanics from 11% in 2009 to 15% in 2019 (P = 0.01) and a declining trend for Blacks from 10% in 2009 to 5% in 2019 (P = 0.01). These racial differences are important as we advocate for the need for aggressive public health

Table 5 Predictors of all-cause inpatient mortality for non-alcoholic fatty liver disease hospitalizations with peptic ulcer disease in the United States from 2009-2019

Variable	Adjusted hazard ratio	95% confidence interval	*P* value
Coagulopathy	2.24	2.14-2.34	< 0.001
Obesity	0.79	0.74-0.84	< 0.001
Protein calorie malnutrition	1.16	1.11-1.22	< 0.001
Fluid and electrolyte disorder	1.92	1.82-2.01	< 0.001
Alcohol abuse	1.51	1.42-1.61	< 0.001
Perforation	2.71	1.37-5.35	0.004

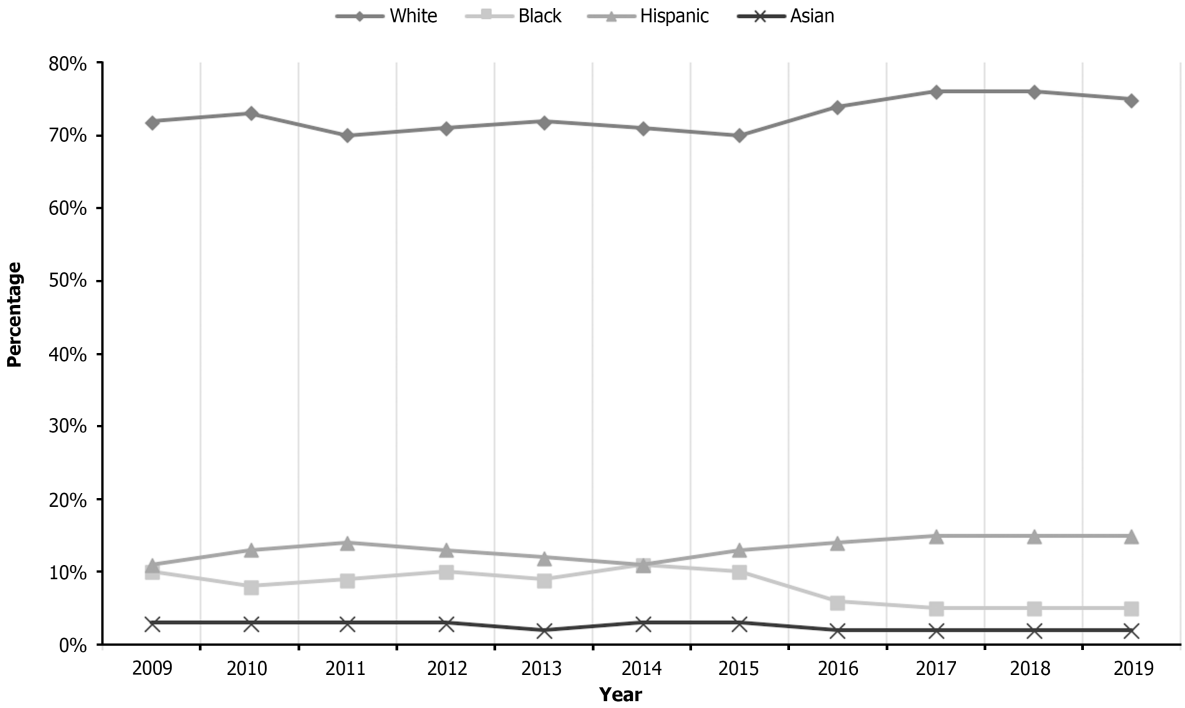

Figure 1 Racial trends for non-alcoholic fatty liver disease hospitalizations hospitalizations with peptic ulcer disease in the United States from 2009-2019.

measures for Hispanic populations to increase awareness about the burden of PUD in those who have NAFLD. Moreover, hospitalists and gastroenterologists who take care of NAFLD hospitalizations should have a high degree of suspicion of PUD in these patients.

In the United States, there has been a significant increase in inpatient mortality for NAFLD-cirrhosis by 32% between 2005-2015, despite a decrease in the inpatient mortality rates for patients with all other causes of liver cirrhosis[19]. However, there has been a significant decline in inpatient PUD mortality due to the increasing use of therapeutic endoscopic procedures for bleeding ulcers[20]. In our study, there was a rising trend of all-cause inpatient mortality for NAFLD hospitalizations with PUD (Table 2). From a race perspective, we noted an increasing trend of all-cause inpatient mortality for Blacks and Hispanics, while a decline was observed for Whites. The exact reasons for these findings are unknown, but they may, in part, be attributed to a higher comorbidity burden and the increasing mean age for NAFLD hospitalizations with PUD, particularly for ethnic minorities *i.e.,* Blacks and Hispanics (Table 1), leading to greater severity of disease and adverse outcomes. Interestingly, we noted lower all-cause inpatient mortality, mean LOS, and mean THC for NAFLD hospitalizations with PUD compared to non-NAFLD PUD hospitalizations, despite a higher comorbidity burden. But there was no statistical difference in the proportion of patients with complications such as GI bleeding and perforation between the two groups. The exact reason for this protective effect of NAFLD is unclear and needs further investigation by multi-center prospective studies.

There has been a rapid decline in *H. pylori* infection rates in the western world secondary to higher standards of living and improved hygiene[21]. An analysis of outpatient endoscopy centers in the United States noted a significant fall in *H. pylori* infections from 11% in 2009 to 9% in 2018[22]. However,

a recent cross-sectional study identified a positive relationship between *H. pylori* infection and NAFLD in females after adjusting for metabolic variables, gastrin factors, and liver enzymes[23]. This implies that rates of *H. pylori* infection may rise with an increasing prevalence of NAFLD. Our study contradicts these findings as we observed a declining trend of *H. pylori* infection in NAFLD hospitalizations with PUD (Table 1). Furthermore, we also noted a decline in the trends of utilization of upper endoscopy from 60% in 2009 to 19% in 2019. This may be due to increased adherence to guideline-directed management which advocates for non-endoscopic testing for uninvestigated dyspepsia without alarm features in individuals < 60 years of age[24]. However, due to an increasing trend of all-cause inpatient mortality in this subset population, it may be justified to perform upper endoscopy at an early stage to prevent adverse clinical outcomes. Interestingly, NAFLD hospitalizations with PUD had a higher proportion of patients that underwent upper endoscopy compared to non-NAFLD PUD hospitalizations. The exact reason for this is currently unknown and needs further investigation.

Our study has numerous strengths and some limitations. A key strength of this study is the study population, which is derived from one of the largest, publicly available, all-payer, multi-ethnic databases in the United States. An analysis over the 11-year study period allowed us to obtain meaningful information on the trends of hospitalization characteristics and outcomes for NAFLD hospitalizations with PUD, adding to scarce literature. Moreover, through our unique and multifaceted comparative analysis, we were able to determine the influence of NAFLD on PUD. Furthermore, as the NIS database covers 97% of the United States population, the results of our study are applicable to almost all NAFLD hospitalizations with PUD, offering a national perspective. However, we do acknowledge the limitations associated with our study. This was a retrospective study design which is subject to all biases associated with retrospective studies. The NIS database does not contain information on the severity, time from hospitalization to discharge, hospital course, and other treatment aspects of the disease. Lastly, the NIS is an administrative database maintained through data collection organizations that use the ICD coding system to store inpatient data. Hence, the possibility of human coding errors cannot be excluded. However, despite these limitations, we believe that the large sample size and a comprehensive analysis technique help us better understand the trends, characteristics, and outcomes of NAFLD hospitalizations with PUD, and promote future research on the topic.

CONCLUSION

NAFLD is a public health concern and places a significant burden on the United States healthcare system. There is a significant knowledge gap on PUD in patients with NAFLD who are admitted to the hospital. We noted an increase the all-cause inpatient mortality for NAFLD hospitalizations with PUD in the United States between 2009-2019. There was a rising trend of NAFLD hospitalizations with PUD for Hispanics, reflecting the need for urgent public health measures to increase awareness in this subset population. Compared to non-NAFLD PUD hospitalizations, NAFLD hospitalizations with PUD had lower inpatient mortality, mean LOS, and mean THC despite a higher comorbidity burden. However, there was no statistical difference in GI bleeding and perforation between the two groups. Perforation of the GI tract, coagulopathy, alcohol abuse, malnutrition, and fluid and electrolyte disorders were identified to be independent predictors of all-cause inpatient mortality for NAFLD hospitalizations with PUD. Additional multi-center prospective studies are needed to further confirm these findings.

ARTICLE HIGHLIGHTS

Research background

The association between peptic ulcer disease (PUD) and liver cirrhosis has been thoroughly investigated. However, there are knowledge gaps on PUD in non-alcoholic fatty liver disease (NAFLD) hospitalizations. As the prevalence of NAFLD continues to rise across the globe and in the United States, it is vital to identify individuals with NAFLD at high risk of adverse clinical outcomes from PUD.

Research motivation

In current literature, there is a knowledge gap on PUD in NAFLD hospitalizations. Hence, this study was designed to help fill the knowledge gaps that currently exist in this subset population.

Research objectives

Our main objective was to identify national trends in hospitalization characteristics, clinical outcomes, and complications for NAFLD hospitalizations with PUD. We also performed a comparative analysis between NAFLD and non-NAFLD hospitalizations with PUD to assess the influence of NAFLD on PUD.

Research methods

The National Inpatient Sample was used from 2009-2019 to identify all adult (≥ 18 years) NAFLD hospitalizations with PUD in the United States. Furthermore, a control group of all adult PUD hospitalizations without NAFLD were identified for comparative analysis. Statistical analysis was conducted using SAS 9.4. To test for the trend for proportions of binary variables, the Cochran-Armitage trend test was implemented. The trend for the averages of continuous variables in years was examined using linear regression. The Rao-Scott design-adjusted chi-square test examined the association between two categorical variables.

Research results

NAFLD-PUD hospitalizations increased from 3745 (2009) to 3805 (2019). Racial differences were noted as NAFLD hospitalizations with PUD increased for Whites and Hispanics, while a decline was observed for Blacks and Asians. There was an increase in all-cause inpatient mortality for NAFLD hospitalizations with PUD from 2% in 2009 to 5% in 2019 ($P < 0.001$). However, the rates of *Helicobacter pylori* (*H. pylori*) infection and upper endoscopy decreased during the study period. Despite a high comorbidity burden, we observed lower inpatient mortality, mean length of hospital stay, and mean total healthcare cost (THC) for NAFLD-PUD hospitalizations *vs* the non-NAFLD-PUD cohort. Perforation of the gastrointestinal tract, coagulopathy, alcohol abuse, malnutrition, and fluid and electrolyte disorders were identified as independent predictors of inpatient mortality for NAFLD hospitalizations with PUD.

Research conclusions

Between 2009-2019, inpatient mortality for NAFLD hospitalizations with PUD increased. However, there was a significant decline in *H. pylori* infections and esophagogastroduodenoscopy for NAFLD-PUD hospitalizations. After a comparative analysis, NAFLD-PUD hospitalizations had lower rates of mortality, mean length of hospital stay, and mean THC *vs* the non-NAFLD-PUD cohort despite a higher comorbidity burden.

Research perspectives

This is one of the few national studies which investigates trends, clinical outcomes, and complications of NAFLD hospitalizations with PUD, using one of the largest, multi-ethnic databases in the United States. Future research should be directed toward identifying the underlying cause of racial disparities for this subset population.

FOOTNOTES

Author contributions: Dahiya DS, Ali H, Inamdar S, Sanaka MR, and Al-Haddad M were responsible for the conception and design; Dahiya DS, Inamdar S, Sanaka MR, and Al-Haddad M provided administrative support; Dahiya DS and Ali H were responsible for provision, collection, and assembly of data; all authors were responsible for review of literature, drafting the manuscript, and revision of key components of the manuscript; and all authors have read and approve the final version of the manuscript.

Institutional review board statement: The National Inpatient Sample database contains numerous safeguards to protect patient privacy. It also lacks patient- and hospital-specific identifiers. Therefore, our study was exempt from Institutional Review Board (IRB) evaluation as per guidelines put forth by our institutional IRB for analysis of HCUP databases.

Informed consent statement: The data for this study was collected from the National Inpatient Sample (NIS) database. As the NIS database lacks patient-specific and hospital-specific identifiers, this study did not require informed consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The National Inpatient Sample is a publicly available database that can be accessed at https://www.hcup-us.ahrq.gov. Due to the availability of a large sample size within the NIS database, it is an ideal choice for the estimation of national trends and clinical outcomes.

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ORIGINAL ARTICLE

Observational Study

Clinicopathological features of 11 cases of chronic hepatitis B infection complicated with primary biliary cholangitis

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Abstract

BACKGROUND

Only a few cases of chronic hepatitis B (CHB) with primary biliary cholangitis (PBC) have been reported based on histological evidence from liver biopsies.

AIM

To observe the clinicopathological features and outcomes of 11 patients with CHB infection complicated by PBC.

METHODS

Eleven patients with CHB and PBC who underwent liver biopsy at the Zhenjiang Third Hospital, affiliated with Jiangsu University, and Wuxi Fifth People's Hospital, from January 2005 to September 2020, were selected. All patients initially visited our hospital with CHB and were pathologically diagnosed with CHB and PBC.

RESULTS

Only five had elevated alkaline phosphatase levels, nine were positive for anti-mitochondrial antibody (AMA)-M2, and two were negative for AMA-M2. Two had jaundice and pruritus symptoms, 10 had mildly abnormal liver function, and one had severely elevated bilirubin and liver enzyme levels. The pathological characteristics of CHB complicated by PBC overlapped with those of PBC-autoimmune hepatitis (AIH). When necroinflammation of the portal area is not obvious, the pathological features of PBC are predominant, similar to the features of PBC alone. When the interface is severe, biliangitis will occur, with a large number of ductular reactions in zone 3. Unlike the PBC-AIH overlap pathology, this pathology is characterized by a small amount of plasma cell infiltration. Unlike PBC, lobulitis is often observed.

CONCLUSION
This is the first large case series to show that the rare pathological features of CHB with PBC are similar to those of PBC-AIH and small duct injury was observed.

Key Words: Chronic hepatitis B; Primary biliary cholangitis; Clinicopathological features; Anti-mitochondrial antibody

Core Tip: We retrospectively observed the clinicopathological features and outcomes of 11 patients with chronic hepatitis B (CHB) infection complicated by primary biliary cholangitis (PBC). We found that CHB complicated with PBC had pathological characteristics overlapping with PBC-autoimmune hepatitis. When necroinflammation of the portal area is not obvious, the pathological features of PBC are superior, similar to the features of PBC alone, this pathology is characterized by a small amount of plasma cell infiltration. Unlike PBC alone, lobulitis is often present. All patients improved after antiviral and ursodeoxycholic acid treatment and stabilized after 1 year.

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INTRODUCTION

Chronic hepatitis B (CHB) remains the largest public health burden in China, with nearly 60 million people infected with the CHB virus and nearly 300000 deaths related to liver disease every year[1,2]. Primary biliary cholangitis (PBC) is a slowly progressing autoimmune disease that is prevalent in Northern Europe and North America. PBC remains uncommon compared with CHB in Asian populations. Large cohort studies have reported that, in Japan and Hong Kong, only 2.4% and 1.3% of PBC cases occur in patients with chronic liver disease, respectively[3]. A recent study from southern China reported that PBC occurred in 49.2 cases out of 100000 adults who underwent routine annual examinations[4]. Anti-mitochondrial antibody (AMA)-M2 was reported in 22 of the 325 patients (6.8%) with CHB[5]. A positive AMA result did not confirm the presence of PBC. Only a few cases of CHB with PBC based on histological evidence from liver biopsies have been reported. We retrospectively examined the clinicopathological features and outcomes of 11 patients with CHB complicated by PBC.

MATERIALS AND METHODS

Methods

Eleven cases of CHB patients with PBC who underwent liver biopsy were all at the Third People's Hospital of Zhenjiang City and the Fifth People's Hospital of Wuxi City from January 2005 to September 2020. CHB infected persons were defined as hepatitis B surface antigen (HBsAg) lasting for more than half a year. PBC was diagnosed if two of the following three criteria were met: (1) Biochemical abnormalities reflecting cholestasis, such as elevated alkaline phosphatase (ALP) and γ-glutamyl transferase (GGT) levels given that extra- or intrahepatic bold tube obstruction is excluded by imaging examination; (2) positive serum AMA/AMA-M2 or other PBC-specific autoantibodies such as anti-GP210 and anti-SP100; and (3) histological evidence of chronic non-suppurative destructive cholangitis (CNSDC) and interlobular bile duct destruction in liver biopsy[6]. The exclusion criteria were a history of excessive alcohol consumption (defined as ≥ 20 g/d for men and ≥ 10 g/d for women)[7], drug-induced hepatitis, schistosomiasis liver disease, autoimmune hepatitis (AIH), or hepatitis A, C, or D. This study was approved by the Ethics Committee of The Third People's Hospital of Zhenjiang City.

Data collection

The following demographic data (sex and age) were collected: clinical history (medical history, drinking history, family history); antiviral treatment status; results of routine blood tests; biochemical indicators; hepatitis B pathogenic serological examination; and tumor indicators during liver biopsy, including total bilirubin, albumin, prealbumin, alanine aminotransferase, aspartate aminotransferase, GGT, ALP, platelet count, HBsAg, hepatitis B e antigen, hepatitis B virus (HBV) DNA level, alpha-fetoprotein,

indicators of other types of viral hepatitis, human immunodeficiency virus antibody, and autoantibody examination results; antibodies (AMA) and subtypes (AMA-M2), antibodies against gp210, sp100, and immunoglobulins G (IgG) and M (IgM).

Pathological assessment

Liver biopsies were performed using a 16G puncture needle (Bard Peripheral Vascular Inc., United States) under ultrasound guidance by an experienced hepatologist. The length of the puncture tissue was greater than 1.5 cm and the tissue was fixed in formalin. The tissues were evaluated by two liver pathologists using the METAVIR and Ludwig staging systems[8,9].

RESULTS

Clinical features

There were 11 cases of CHB diagnosed with PBC, of which four were male and seven were female, with an average age of 42 years (range, 28-60 years); nine cases were positive for AMA-M2. Two AMA-M2-negative patients with elevated ALP and GGT levels but without other etiological explanations were diagnosed with PBC by liver biopsy. ALP levels were elevated in five of the 11 cases. Six patients had normal ALP levels, while four had elevated GGT levels and positive AMA-M2 results. Two patients attained a complete HBV response (HBV DNA < 10 U/L) before liver biopsy, and the remaining patients with CHB underwent primary antiviral treatment, with five receiving entecavir, three receiving tenofovir, and three receiving propofol tenofovir fumarate. Patient 7 was hospitalized for severe liver injury for approximately 2 mo. After control was achieved, patient 7 received outpatient treatment similar to that of the other patients (Table 1).

Pathological characteristics

The lesions were primarily caused by necroinflammation of the portal tract. All cases showed bile duct injury; five showed a typical florid duct lesion (FDL) and three cases with severe interfacial necroinflammation showed PBC-AIH-like injury with fewer plasma cells. A ductular reaction was evident that extended deep into the hepatocyte plate, and bile duct interfacial necroinflammation was apparent. Six patients with normal ALP and AMA-M2 expression had bile duct injuries. Overall, the METAVIR staging was consistent with the Ludwig staging (Table 2, Figure 1).

Treatments and outcomes

Three patients with CHB had previously received antiviral therapy, and eight patients with HBV DNA-positive liver biopsies received antiviral therapy. The antiviral drugs used were entecavir in five cases, tenofovir in three cases, and propofol tenofovir in three cases. Ten patients experienced viral remission (< 10 U/L) after six months, and one experienced viral remission after one year. ALP levels returned to normal in four of the five patients with elevated ALP levels, and one patient returned to normal levels. Of the eight patients with elevated GGT levels, seven returned to normal after six months and one returned to normal after one year (Table 3).

DISCUSSION

Hepatitis B is a lifelong immune-related disease. Raynaud's phenomenon occurs in 2% of patients with CHB, arthralgia or arthritis in 3%, myalgia in 3%, Sjögren's syndrome in 3%, glomerulonephritis in 3%, uveitis in 2%, and cryoglobulin in 2%[10]. In a Chinese study on the detection rate of autoantibodies against CHB, 58.2% of patients with CHB were found to have AMA-M2 (approximately 7%)[5]. The 11 patients in our study were selected from approximately 1500 CHB liver histology examiners at two centers. The AMA-M2 positivity rate was < 1%, which may be related to the fact that many patients did not undergo the AMA-M2 examination.

Logically, preclinical PBC refers to patients with positive AMA but normal enzymatic indicators (*i.e.*, ALP and GGT) that reflect cholestasis and no PBC manifestation on histology who nonetheless progress to PBC during follow-up. A prospective multicenter cohort study in France[11] found a 5-year incidence of PBC of 16% in a population with positive AMA and normal ALP levels. A recent single-center study in Austria[12] reported that, after an average follow-up of 5.8 years, only 10.2% of 122 AMA-positive patients developed PBC. An earlier study also found that only one (4%) of 26 AMA-positive first-degree relatives with normal ALP levels developed PBC after an 8-9-year follow-up[13].

In most reported cases, the diagnosis of PBC in patients with CHB is delayed for many years[14]. All 11 patients initially visited the hospital because of CHB, and eight patients were found to be AMA-M2 positive during the course of treatment. Of these, two with CHB showed ALP elevation after antiviral treatment, and a bile duct injury was detected by liver puncture. Only two patients had jaundice and pruritus symptoms, ten had mild abnormal liver function, and one patient had very serious increases in

Table 1 Clinical characteristics of 11 cases of chronic hepatitis B complicated with primary biliary cholangitis

No.	Sex	Age	TBIL	ALT	AST	ALP	GGT	TBA	Albumin (g/L)	AMA-M2	gp120	sp100	ANA	IgM	IgG	HBV DNA (Log)	Platelet (1 × 10^9 /L)	Fatigue	Pruritus
1	Woman	42	22.2	87	56	47	67	17	32.2	++	+	-	+	4.25	21.15	7.21	9.21	+	+
2	Man	60	45.2	224	175	154	116	30	36.5	+	-	-	-	1.25	11.23	4.25	12.66	-	-
3	Woman	52	13.5	35	24	57	57	12	41.2	+	-	-	-	1.65	9.32	4.68	8.35	-	-
4	Man	37	15.5	22	16	46	47	8	38.2	+	-	-	-	1.42	8.65	5.32	16.35	-	-
5	Man	39	16.0	35	24	65	37	12	37.9	+	-	-	-	1.87	10.32	-	15.32	-	-
6	Woman	37	16.3	27	18	74	58	14	36.4	++	-	-	-	2.01	11.56	6.14	11.25	-	-
7	Man	57	422.4	243	215	767	837	147	32.2	+	-	-	-	4.36	24.32	4.35	13.65	+	+
8	Woman	52	20.4	156	87	167	224	25	40.2	++	+	-	+	0.98	10.48	3.57	14.25	+	-
9	Woman	32	11.3	25	11	37	26	37	41.6	+	-	-	-	1.14	9.65	4.25	24.22	-	-
10	Woman	28	32.7	18	15	166	89	18	39.2	-	-	-	-	1.58	13.64	-	21.03	-	-
11	Woman	51	25.6	87	26	185	98	9	38.1	-	-	-	-	1.67	10.35	-	18.21	-	-

TBIL: Total bilirubin; TBA: Total bile acid; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyltransferase; ALP: Alkaline phosphatase; AMA-M2: Antimitochondrial antibody and subtypes-M2; ANA: Antibodies against gp210, antibodies against sp100, antinuclear antibodies; Ig: Immunoglobulin.

Table 2 Changes of biochemical indexes before and after treatment

	TBIL	ALT	AST	ALP	GGT	TBA	IgM	IgG
Before treatment	20.4 (11.3-422.4)	35 (18-243)	24 (11-215)	66 (37-767)	58 (17-837)	17 (8-147)	1.65 (0.98-4.37)	12.7 (8.6-24.3)
After treatment	17.7 (6.7-21.2)	27 (12-63)	21 (15-43)	47 (38-107)	25 (16-42)	9 (6-20)	1.4 (1.1-2.5)	11.3 (6.8-15.3)
Statistical value	1.223	2.351	1.656	1.326	2.369	1.632	2.435	0.931
P value	0.248	0.041	0.129	0.214	0.039	0.134	0.031	0.374

TBIL: Total bilirubin; TBA: Total bile acid; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyltransferase; ALP: Alkaline phosphatase; Ig: Immunoglobulin.

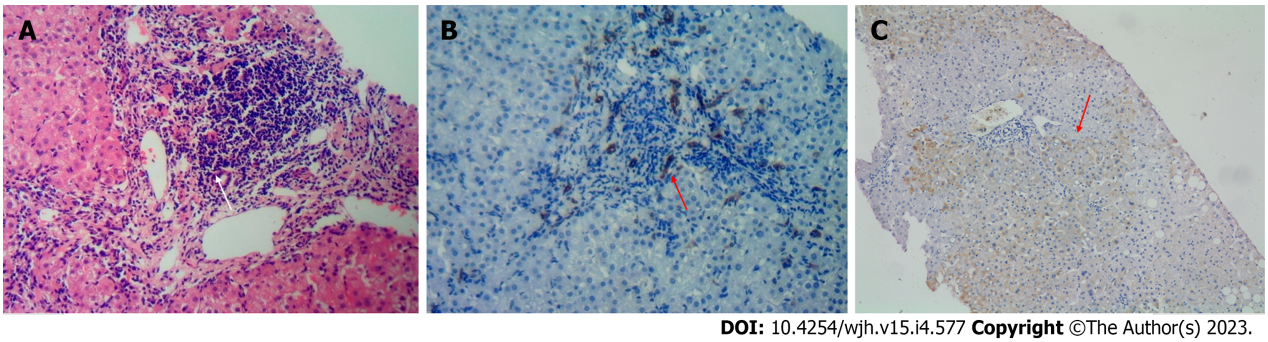

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Figure 1 Histological characteristics of liver in patient 3. A: Severe necroinflammation of the portal tract, chronic non-suppurative cholangitis and florid duct injury (arrow); B: CK7 staining showed interfacial ductular reaction (arrow); C: Hepatitis B surface antigen staining showed hepatitis B infection (arrow).

bilirubin and liver enzyme levels that rapidly improved after antiviral and ursodeoxycholic acid (UDCA) treatment; liver histology showed severe necrosis and fibrosis.

In a recent single-center study in China, up to 80% of patients positive for AMA and with normal ALP were pathologically confirmed to have PBC[15], which is similar to the findings of a multicenter study in Switzerland[16]. Both studies[15,16] suggested that a high AMA titer and elevated IgM and ALP levels close to the upper limit of normal are predictive factors for PBC expression on histology.

Table 3 Pathological characteristics of 11 cases of chronic hepatitis B complicated with primary biliary cholangitis

No.	II	BN	LI	DI	FDL	BIH	DU	HBsAg staining	HBcAg staining	METAVIR activity score	METAVIR stage	Ludwig stage
1	1	-	2	+	+	-	-	+	+	2	F1	I
2	1	-	1	+	-	-	-	-	-	1	F1	II
3	0	-	1	+	+	-	-	+	-	1	F1	I
4	2	+	2	+	-	+	-	-	+	2	F1	II
5	0	-	1	+	+	-	-	+	-	1	F2	I
6	1	-	1	+	-	+	-	+	-	1	F1	I
7	3	+	2	+	+	+	-	+	+	3	F3	II
8	2	+	1	+	-	+	-	-	-	2	F1	I
9	1	-	1	+	-	+	+	+	-	1	F4	III
10	0	-	0	+	+	-	-	-	-	0	F0	I
11	1	-	1	+	-	-	-	+	-	1	F0	I

II: Interfacial inflammation; BN: Bridging necrosis; LI: Lobular inflammation; DI: Ductal injure; FDL: Florid duct lesion; BIH: Biliary interface hepatitis; DU: Ductopenia; HBsAg: Hepatitis B surface antigen; HBcAg: Hepatitis B core antigen.

Notably, despite normal ALP levels, GGT levels were elevated in most patients in our study. In our 11 cases, only five had elevated ALP, and only three were AMA-M2 positive; nine cases were AMA-M2 positive, seven cases had elevated GGT, and only three cases had elevated ALP. For cases of CHB that are AMA-positive, even though ALP and GGT levels are normal, PBC is likely to be combined; therefore, it cannot be considered that CHB has autoantibodies at present. Changes in liver biochemical indicators in this population should be monitored every year, and for patients with elevated IgM and GGT levels, liver biopsy should be considered to determine the presence of PBC.

The pathological characteristics of CHB is primarily characterized by necroinflammation of the portal tract and lobular inflammation. Bridge-like multilobular necrosis can also occur in severe cases. Fibrosis usually occurs in the portal tract and gradually bridges the adjacent portal areas to form a package. The pathological characteristics of CHB are nonspecific and are difficult to differentiate from those of other chronic liver injuries. The main pathological feature of PBC is CNSDC, involving the interlobular bile duct (small bile duct). The characteristic lesion is the infiltration of lymphocytes around the bile duct and the formation of epithelioid granulomas, which is called incandescent cholangiopathy (FDL). When no small bile ducts were accompanied by a small artery in > 50% of the portal area, it was defined as a reduction or disappearance of the bile duct. Ludwig *et al*[8] divided PBC into four phases. We found that CHB combined with PBC had overlapping pathological characteristics similar to those of PBC-AIH. When necroinflammation in the portal area is not evident, the pathological characteristics of PBC are predominant over those of simple PBC. In contrast, when the interface inflammation is serious, cholangio interface inflammation occurs, and a large number of ductular reactions occur in zone 3. The overlapping pathological feature that differs from that of PBC-AIH is the small amount of plasma cell infiltration. Compared with simple PBC[8], lobular inflammation often occurs; 10 cases had lobular inflammation, and three cases were more serious. FDL are characteristic PBC lesions that do not always occur in patients with CHB or PBC. FDL was observed in five cases in Scheuer's original report[17]. CNSDC has also been observed in the livers of patients with nodular cirrhosis. Additionally, the pathology of PBC is not always evenly distributed in the liver; therefore, sampling errors may occur when determining the stage of these systems.

Currently, there are no cohort observations of CHB overlapping with PBC. A Chinese study surveyed 379 HBsAg-negative patients with PBC, 52 of whom underwent a liver biopsy. The enrolled patients were divided into the anti-HBC-positive and anti-HBC-negative groups. Histological examination revealed that patients in the anti-HBC-positive group had more advanced PBC than those in the anti-HBC-negative group ($P < 0.05$)[18]. In a single-center retrospective review of all follow-up HBV (n = 1493) and hepatitis C virus (HCV; n = 526) patients[14], 17 were identified as having concurrent viral hepatitis and PBC, and most were found to have cirrhosis (10/17, 58.8%). The authors speculated that chronic viral hepatitis combined with PBC was a risk factor for cirrhosis; however, the diagnosis of PBC was mainly based on the presence of anti-mitochondrial antibodies and elevated cholesterol levels. Only one of our 11 patients was diagnosed with cirrhosis. After treatment, the disease was quickly controlled, and the liver transaminase levels stabilized and were normal. All patients achieved biochemical normality within one year. However, the aforementioned pathological characteristics of HBV infection combined with PBC suggest that, as observed in these cohort studies, HBV infection combined with

PBC is more prone to disease progression.

CONCLUSION

The shortcomings of this cohort study are its small sample size and descriptive nature. Nevertheless, this is the first large case series to show that the rare pathological features of CHB with PBC are similar to those of PBC-AIH. Although ALP was normal in nearly 50% of patients, small duct injury was observed, and all patients responded effectively after antiviral and UDCA treatment. The lack of overlap between these two diseases is an aggravating phenomenon.

ARTICLE HIGHLIGHTS

Research background

Chronic hepatitis B (CHB) and primary biliary cholangitis (PBC) are chronic liver diseases; however, CHB combined with PBC is uncommon.

Research motivation

There are few studies on the clinical and pathological characteristics of CHB combined with PBC, and current research is limited to case reports.

Research objectives

To explore the clinicopathological characteristics, diagnoses, and treatments of patients with CHB and PBC.

Research methods

Eleven patients with chronic hepatitis B virus (HBV) infection and PBC who underwent liver biopsy at our hospital between January 2005 and September 2020 were selected. Demographic data, clinical biochemical indicators, autoantibodies, and virological indicators were also collected. The liver pathology was evaluated using the METAVIR and Ludwig staging systems.

Research results

Eleven patients with CHB were diagnosed with PBC, and nine were anti-mitochondrial antibody-M2 positive. Alkaline phosphatase (ALP) increased in five of the 11 cases. ALP levels were normal in six patients, but γ-glutamyl transferase levels were elevated in four patients. Pathological changes were primarily caused by inflammation of the portal area. All cases showed bile duct injury, five cases showed a typical florid duct region, and three cases with severe interfacial inflammation showed similar autoimmune hepatitis-PBC-like injury with few plasma cells. All the patients received antiviral and ursodeoxycholic acid treatment.

Research conclusions

For the first time, the pathological characteristics of rare CHB complicated with PBC were observed in a large sample size. A normal ALP level cannot exclude the diagnosis of PBC. The pathological characteristics were similar to those of PBC-autoimmune hepatitis, but with fewer plasma cells.

Research perspectives

Attention should be paid to the possibility of HBV combined with PBC. Pathology can provide important information, even if biochemical changes or specific antibodies are negative.

FOOTNOTES

Author contributions: Ye Y, Zhang Q, and Lu ZH contributed equally to the research; Tan YW and Ye Y designed the research; Zhang Q and Lu ZH collected and analyzed the data and drafted the manuscript; Tan YW performed the liver pathological evaluations; Tan YW and Ye Y wrote and revised the manuscript; all authors read and approved the final version for publication.

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