



## Review Article

# The Clinical Significance of Lipids/Lipoproteins Impairment in the Context of Cirrhosis: An Updated Review



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## Abstract

The liver contributes substantially to the metabolic transformation and transport of lipids and lipoproteins. These bioactive substances represent a heterogeneous group of molecules with pivotal roles in diverse pathological processes as well as disease progression, the advent of complications, and the response to specific treatments in the context of cirrhosis. The present mini-review aims to summarize the underlying mechanisms regarding lipid changes across divergent circumstances. Recent evidence suggests the prognostic value of lipids/lipoproteins and their close relationship to an increased risk for morbidity and mortality among cirrhotic patients. However, more research regarding the development of risk stratification and therapeutic strategies based on altered lipid profiles in patients with cirrhosis is warranted.

## Introduction

Liver cirrhosis represents an advanced stage of various chronic liver diseases. Chronic hepatitis B virus (HBV) or C virus (HCV) infection, alcohol overuse, and nonalcoholic fatty liver disease (NAFLD) are among the most common etiologies of cirrhosis. Liver dysfunction and portal hypertension in cirrhotic patients can lead to a wide spectrum of complications, such as ascites, gastro-

intestinal bleeding, hepatic encephalopathy, and bacterial infection.<sup>1,2</sup> Liver cirrhosis is one of the leading causes of death globally and is responsible for 1 million deaths annually.<sup>1</sup>

The liver plays a fundamental role in the synthesis, storage, and metabolic processing of lipids/lipoproteins. Given the space limitation of this mini-review, the explicit and comprehensive information regarding key metabolic pathways and principle bio-transformation routes pertinent to lipids/lipoproteins can be found elsewhere.<sup>3,4</sup> When liver function is substantially impaired, lipid and lipoprotein homeostasis will undergo imbalance and lose maintenance.<sup>5</sup> Multiple studies have acknowledged serum lipids as important risk factors for the progression of liver cirrhosis.<sup>6–8</sup> Collectively, this review article summarizes the accumulative understanding of the relationship between the serum lipids/lipoproteins profile and cirrhosis.

## Pathophysiology and mechanism of lipid changes in cirrhosis

Since the underlying mechanism pertaining to lipid changes in cirrhosis is complicated and currently undergoing extensive investigations, we herein highlight several possible issues including gene polymorphisms, signaling pathways, the molecular basis, and emerging mechanism (Fig. 1). Alcohol abuse is a remarkable risk factor for alcoholic liver cirrhosis (ALC). In this regard, acetaldehyde dehydrogenase 2 (ALDH2) is the key rate-limiting enzyme responsible for alcohol metabolism, and the level of ALDH2 activity is intrinsically linked to the advent of alcohol-related liver disease. The most important single nucleotide polymorphism (SNP)

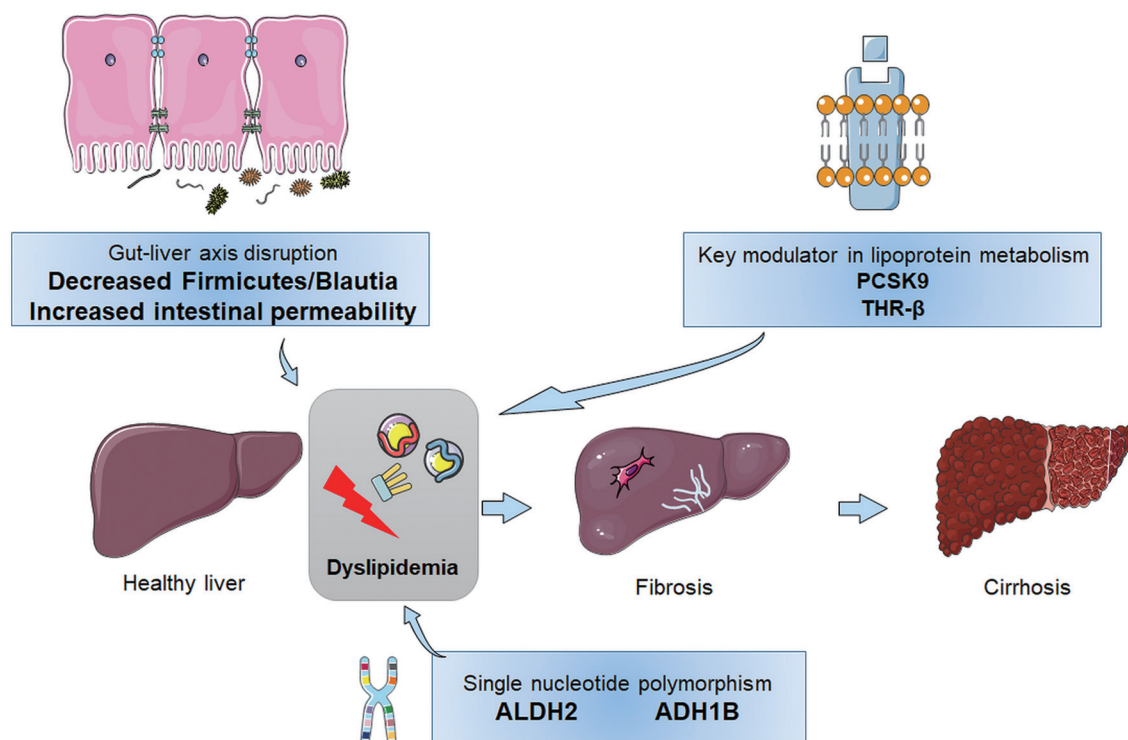
**Keywords:** Lipid; Lipoprotein; Liver cirrhosis; Complication; Mortality; HDL-C.

**Abbreviations:** ADH1B, alcohol dehydrogenase-1B; ALDH2, acetaldehyde dehydrogenase 2; apoA-I, apolipoprotein A-I; apoE, apolipoprotein E; daclatasvir; EV, esophageal varices; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; LP-Z, lipoprotein-Z; MELD, Model for End-stage Liver Disease; NASH, nonalcoholic steatohepatitis; PCSK9, proprotein convertase subtilisin/kexin type 9; PSVT, portal and/or splenic vein thrombosis; RAI, relative adrenal insufficiency; SNP, single nucleotide polymorphism; SOF, sofosbuvir; TC, total cholesterol; TG, triglyceride; THR-β, thyroid hormone receptor beta; UGIB, upper gastrointestinal bleeding; VLDL, very-low-density lipoprotein.

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**Fig. 1. The underlying mechanism pertaining to lipid changes in cirrhosis appears to be complicated.** Gene polymorphisms (single nucleotide polymorphisms) prone to the progression of cirrhosis and the abnormal expression of critical molecules involved in lipid (lipoprotein) metabolism or disruption regarding the gut-liver axis may be responsible for dyslipidemia in the context of cirrhosis. ADH1B, alcohol dehydrogenase-1B; ALDH2, acetaldehyde dehydrogenase 2; PCSK9, proprotein convertase subtilisin/kexin type 9; THR- $\beta$ , thyroid hormone receptor beta.

in the *ALDH2* gene is the Glu504Lys polymorphism (SNP rs671, G>A, GAA>AAA), and the *ALDH2* rs671 G>A SNP polymorphism has been proven to be a susceptibility site to develop ALC in the southern Chinese Hakka population.<sup>9</sup> The levels of high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and apolipoprotein A-I (apoA-I) were higher among patients with ALC and the G/A genotype in comparison with those with the G/G genotype, while the levels of HDL-C and apoA-I were lower in patients with the G allele in comparison with those with the A allele. Generally, ALDH2 can affect the serum lipid levels through the regulation of oxidative stress *in vivo*; therefore, gene variation may give rise to dyslipidemia.<sup>10,11</sup> Another study in Japan showed that drinkers with the alcohol dehydrogenase-1B (ADH1B) His allele had lower low-density lipoprotein cholesterol (LDL-C) levels than those with the Arg/Arg genotype.<sup>12</sup> One possible explanation is the expedited clearance of acetaldehyde-modified very low-density lipoprotein (VLDL) and reduced conversion of modified VLDL to LDL.<sup>13</sup> The authors also found that both the ADH1B Arg/Arg and ALDH2 Glu/Lys dominant models were related to higher serum HDL-C levels and lower triglyceride (TG) levels, in particular, among alcoholic men. The impact of heavy drinking on apolipoprotein and lipoprotein-metabolizing enzymes can partially be attributed to the ADH1B and ALDH2 genotypes.<sup>12</sup>

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a pivotal role in the metabolism of cholesterol and is responsible for facilitating the degradation of LDL-receptor in the lysosome and upregulating the plasma LDL-C level. In a cohort of ALC patients, PCSK9 expression did not show a positive correlation with the serum TC level.<sup>14</sup> Regarding individual cholesteryl ester species,

which were quantified by electrospray tandem mass spectrometry, a negative correlation between PCSK9 and cholesteryl ester 20:5 was demonstrated. The expression of hepatic PCSK9 protein also was positively correlated with the expression of hepatic LDL-receptor protein. These findings suggest that liver function abnormality appears to counteract the effect of PCSK9 on cholesterol metabolism among cirrhotic patients, but the specific mechanism of PCSK9 mediating the degradation of the LDL-receptor protein has not been fully elucidated.

The thyroid hormone receptor beta (THR- $\beta$ ) is mainly expressed in the liver, and its activation has been linked to reduced lipid and increased fat oxidation.<sup>15</sup> A study has revealed that the levels of plasma TC were markedly higher in obese mice with non-alcoholic steatohepatitis (NASH) and fibrosis than in lean controls, and a significant reduction in hepatic TC and TG were observed in mouse models in response to THR- $\beta$  agonist treatment.<sup>16</sup>

There is a growing body of literature concerning the gut-liver axis on the development and progression of various liver diseases. For example, Chen *et al.* found that Firmicutes (the most common gut microbiota) and Blautia were remarkably decreased in chronic liver disease (mainly chronic hepatitis B subjects) and hepatocellular carcinoma (HCC) patients compared to healthy individuals.<sup>17</sup> Moreover, the Spearman correlation analysis showed that the Firmicutes composition was positively associated with the HDL-C level and that the Blautia composition was positively associated with the TG and HDL-C levels. As reported previously, Blautia was proven to be inversely associated with visceral fat accumulation among a healthy Japanese population.<sup>18</sup> Another study indicated that Collinsella had the strongest association with NASH.<sup>19</sup>

Moreover, Collinsella was positively related to the TG and TC levels as well as negatively related to the HDL-C level in patients with NASH, suggesting that Collinsella may affect the host lipid metabolism. Furthermore, Collinsella has been reported to be associated with obesity and circulating insulin levels, thus providing a possible mechanism by which Collinsella contributes to the progression of NAFLD.<sup>20</sup>

### Risk of cirrhosis progression

Wang *et al.* have found that HDL-C is an independent indicator of the onset and development of HBV-related cirrhosis in obese patients.<sup>21</sup> Patients with HDL-C levels <1.03 mmol/L had a 2.21-fold increased occurrence of cirrhosis. Likewise, a prospective observational cohort study by Rao *et al.* demonstrated that patients with HDL-C levels <36.4 mg/dL had a 6-fold higher risk of decompensation within 1 year.<sup>22</sup>

Many studies have shown that the levels of serum lipids progressively decrease in alignment with the deteriorated liver function. For example, Sahlman *et al.* have investigated potential risk factors for advanced nonviral liver disease in the general population and found that both HDL-C and non-HDL-C increased the risk for developing severe liver disease among men.<sup>23</sup> In addition, Tauseef *et al.* have reported that a wide array of lipids, including TC, TG, VLDL, LDL-C, and HDL-C, decreased in correspondence to chronic liver disease ranging from Child-Pugh class A to C.<sup>24</sup> Likewise, another study has shown that the levels of TC and lipoprotein(a) were remarkably lower in cirrhotic patients with decompensated insults than in stable participants; and the levels of TC, LDL-C, HDL-C, and lipoprotein(a) were remarkably lower in cirrhotic patients with Child-Pugh class B/C compared with those with Child-Pugh class A.<sup>25</sup> These findings were also corroborated by Trieb *et al.* in which HDL-C and apoA-I decreased with disease progression, regardless of the cirrhosis etiology.<sup>26</sup> The baseline concentrations of HDL-C and apoA-I were significantly lower in patients with stable cirrhosis compared with healthy individuals, and they further decreased following the onset of acute decompensation and acute-on-chronic liver failure. In contrast, Chrostek *et al.* have proposed that the fractions of cholesterol differ due to the etiology of liver cirrhosis.<sup>5</sup> The concentrations of LDL-C and HDL-C have been demonstrated to be diminished in agreement with the severity of liver damage in patients with non-ALC, whereas the TG concentration decreased among those with ALC. The decreased expression of HDL-C and LDL-C in the context of cirrhosis may be attributed to the impaired synthetic capability of apoA and B.<sup>27</sup> As for the association between lipid metabolism and cirrhosis resulting from NAFLD, Li *et al.* have established a NAFLD-caused cirrhosis model in gerbils and denoted discrepancies with respect to the TG and free fatty acids levels.<sup>28</sup> Notably, these changes were apparent within the fibrosis stage, suggesting that the advent of fibrosis can lead to impairment in lipoprotein synthesis and result in decreased TG export. Moreover, they showed that the cholesterol/HDL-C ratios increased constantly, induced by the high-fat and high-cholesterol diet, and had a good linear relationship with hepatic stellate cell activation and proliferation. Taken together, the cholesterol/HDL-C ratios can be a convenient biomarker for diagnosing and predicting the progression of NAFLD fibrosis.

Apolipoprotein E (apoE) plays a critical role in lipoprotein metabolism and immunoregulation.<sup>29</sup> Three codominant alleles (E2, E3, and E4) in the apoE gene can result in six kinds of genotypes (E2/2, E2/3, E2/4, E3/3, E3/4, and E4/4).<sup>30</sup> Intriguingly, Shen *et al.*

have implicated that apoE, interleukin-6 (IL-6), and the frequency of the E3/3 genotype progressively increase, but IL-2 gradually decreases in alignment with the worsening severity of HBV-related disease.<sup>31</sup> The serum levels of LDL-C are higher in the E3/4 and E4/4 phenotypes relative to the E3/3 or E2/3 phenotype. Besides, high apoE levels are positively correlated with the IL-6 level and inversely correlated with the IL-2 level, indicating the immune abnormalities in HBV infection.

HBV infection is the most important cause for the development of HCC in sub-Saharan Africa and Southeast Asia.<sup>32</sup> Ren *et al.* have found that compared with patients with HBV-related cirrhosis, TC and LDL-C are upregulated in HCC accompanied by hepatitis B cirrhosis.<sup>33</sup> Since both TC and LDL-C are mainly synthesized by the liver, it is proposed that the synthetic function of the liver appears to be better in the HCC group.

### Lipid metabolism changes after HCV eradication

HCV infection is a major health problem worldwide and has a considerable morbidity and mortality. In recent years, HCV treatment has dramatically improved due to the emergence of direct-acting antivirals. Sofosbuvir/daclatasvir (SOF/DCV) is a pan-genotypic regimen that is used to treat chronic hepatitis C patients. A prospective observational study enrolling genotype 2 chronic hepatitis C patients evaluated the treatment effectiveness of SOF/DCV with or without ribavirin in Taiwan.<sup>34</sup> The majority of patients undergoing SOF/DCV/ribavirin treatment had cirrhosis with or without decompensation, and a significant increase in the TC and LDL-C levels after treatment was observed. Another prospective study evaluated the effectiveness of glecaprevir/pibrentasvir treatment and the resultant alterations pertinent to the lipid levels.<sup>35</sup> Relevant findings indicated a remarkable elevation of the TC and LDL-C levels during and after treatment, and the HDL-C levels increased after treatment. The LDL-C/HDL-C ratio increased during treatment but returned to baseline after treatment, and two possible explanations were clarified. One is the restoration of cholesterol synthesis along with improved liver function after the disappearance of HCV, the other is the alleviation of hepatic inflammation associated with elimination of the HCV protein.

Inomata *et al.* intended to investigate the metabolic alterations of iron and lipids in chronic hepatitis C patients or those with HCV genotype 1b infection-related compensated cirrhosis after HCV eradication.<sup>36</sup> They found that increased LDL-C levels were correlated with decreased erythroferrone, ferritin, and alanine aminotransferase levels only in men, suggesting an association between increased LDL-C and mitigated hepatic inflammation and fibrosis in addition to alleviated iron overload. Furthermore, they hypothesized that the principal sex hormone, testosterone, may account for these sex-related differences.

### HDL-related biomarkers predict complications of cirrhosis

#### Upper gastrointestinal bleeding

Upper gastrointestinal bleeding (UGIB), a serious clinical scenario, represents a major cause of morbidity and mortality on account of portal hypertension. Hrabovsky *et al.* found that the serum levels of TC, LDL-C, and HDL-C were significantly decreased in patients with acute UGIB, and further comparisons of the lipid profile in cirrhotic and noncirrhotic patients showed no significant differences with the exception of HDL-C.<sup>37</sup> They concluded

that both the synthetic and absorptive processes may be altered in patients with acute UGIB. Lower expression of markers with respect to cholesterol absorption may also be attributed to disrupted food ingestion in the early phase after hemorrhage. Moreover, the concentration of phytosterols in plasma was low in the above-mentioned study, indicating that cholesterol absorption is considerably changed in patients with cirrhosis.

Insulin resistance represents an early phenomenon during the course of HCV infection and is closely linked to the pathogenesis of hepatic fibrosis. Accordingly, it is suggested to be associated with the development of esophageal varices (EV). A study including 100 compensated HCV cirrhotic patients without diabetes or metabolic syndrome has revealed that an insulin/HDL-C ratio of 0.147 can predict the increased occurrence of EV, with a diagnostic accuracy of 0.822.<sup>38</sup> Similarly, Hanafy *et al.* have reported that VLDL <16.5 mg/dL and an LDL/platelet count ratio >1 can predict advanced fibrosis, the presence of EVs, and endothelial dysfunction among patients with HCV-related cirrhosis.<sup>39</sup>

Moreover, it has been shown that HDL-C values  $\leq 0.54$  mmol/L can predict the 6-week mortality among HBV-related cirrhotic patients with acute gastrointestinal bleeding.<sup>40</sup> Two possible interpretations may account for this condition. First, HDL-C is regarded as a biomarker of liver function, which may further decrease in response to hepatocyte ischemia elicited by anemia and arterial hypotension; second, HDL-C has been identified as a modulator of both intrinsic and extrinsic coagulation cascades by *in-vitro* experiments.<sup>41</sup>

### Portal hypertension

It is widely accepted that cirrhotic patients complicated with portal vein thrombosis are prone to dismal outcomes. HDL-C also has been identified to be independently associated with the 1-year mortality among patients with cirrhosis and portal vein thrombosis.<sup>42</sup> A prospective cohort study including 77 patients who underwent a splenectomy due to portal hypertension indicated that the lipoprotein(a) concentration postoperatively was a reliable predictor of portal and/or splenic vein thrombosis (PSVT).<sup>43</sup> Furthermore, patients with PSVT exhibited higher lipoprotein(a) levels compared to those without PSVT following operation.

### Bacterial infections

Bacterial infections are common causes of hospital re-admissions among patients with cirrhosis, with an estimated prevalence of 25–46%.<sup>44,45</sup> The main infections comprise spontaneous bacterial peritonitis and urinary tract infections. The preponderance of evidence implicates the development of bacterial infections as a consequence of a dysregulated immune system, which advances progressively during the course of cirrhosis.<sup>46,47</sup> Some dysbiosis patterns, like enrichment of Enterococcae/Proteobacteria and depletion of the beneficial Lachnospiraceae, have been linked to the progression of cirrhosis.<sup>48</sup> Moreover, *Enterococci* and Gram-negative bacteria (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*) have been identified as the most frequent species to cause spontaneous bacterial peritonitis via pathological bacterial translocation.<sup>49</sup> The presence of diabetes and low levels of HDL-C have been shown to be risk factors of bacterial infection in the context of HBV-related cirrhosis.<sup>50</sup> However, the mechanisms underlying the combined impact of diabetes and cirrhosis on the pathogenesis of bacterial infections are unclear. It has been proposed that hyperglycemia disturbs the hemostasis of the immune system and facilitates a favorable microenvironment for bacterial growth.<sup>51</sup> HDL-C suppresses macrophage-mediated inflammatory

reactions relying on scavenging cholesterol particles.<sup>52</sup>

### Relative adrenal insufficiency

Recent investigations have shown that cirrhosis would also result in relative adrenal insufficiency (RAI). Patients with RAI are prone to suffer from bacterial infections, sepsis, extrahepatic organ failures, and acute-on-chronic liver failure.<sup>53</sup> Although the pathogenesis of RAI remains elusive, metabolic disorder of cholesterol may play an essential role. Cirrhotic patients have been demonstrated to have significantly lower serum cortisol than noncirrhotic patients.<sup>54</sup> In addition, RAI is closely associated with the severity of liver dysfunction, an increased patient mortality, the synthesis, metabolism, and functional reserve of the liver, as well as a poor prognosis.

Piano *et al.* also have implicated that low levels of HDL-C are independently associated with RAI in acute decompensated cirrhosis.<sup>53</sup> They confirmed that HDL-C may be responsible for a deficit of substrates contributing to steroidogenesis in cirrhosis. Moreover, they raised the possibility that inflammatory cytokines can directly affect adrenal glands or impede the production of steroid competing with adrenocorticotrophic hormone at the receptor level.<sup>55</sup>

Furthermore, Wentworth *et al.* have demonstrated that decreased HDL-C levels and diminished lecithincholesterol acyltransferase activity partially account for the development of RAI in decompensated cirrhotic patients.<sup>56</sup> They proposed that cholesterol metabolism impairment results in inadequate substrate delivery to the adrenal gland, which is responsible for normal steroidogenesis.

### HDL-related biomarkers predict mortality

In a retrospective observational cohort recruiting 191 patients, TC was a significant predictor for mortality in cirrhotic patients, and adding cholesterol to the traditional cirrhosis-specific scoring system, *i.e.*, the Model for End-Stage Liver Disease (MELD) score, could improve the prediction accuracy by 3%.<sup>7</sup> Additionally, Trieb *et al.* have shown that HDL-C <17 mg/dL (0.44 mmol/L) and apoA-I <50 mg/dL indicated a 90-day mortality in cirrhotic patients.<sup>26</sup> Another study also identified HDL-C  $\leq 0.53$  mmol/L as an independent predictor for the 30-day mortality in HBV-related decompensated cirrhotic patients.<sup>8</sup> Based on receiver operating characteristic curve analyses, the prognostic performance for mortality was similar between the HDL-C level and the MELD score. Notably, Cui *et al.* performed propensity score matching analysis to assess the prognostic value of HDL-C for short-term mortality.<sup>6</sup> Their findings denoted that HDL-C <0.4 mmol/L indicated a high 180-day mortality risk in patients with cirrhosis. In addition, the HDL-C level had an incremental value to prognosticate the short-term mortality against the MELD score or Child-Pugh class.

It is well known that inflammation is a common feature in patients with advanced cirrhosis and is associated with inferior outcomes.<sup>57</sup> The monocyte-to-HDL-C ratio is regarded as a recently proposed inflammatory biomarker. An elevated monocyte-to-HDL-C ratio has been shown to be predictive of increased mortality in HBV-related decompensated cirrhotic patients.<sup>58</sup> The potential mechanisms involve that the inflammation triggers monocyte release into the peripheral blood and produces pro-inflammatory molecules, leading to acceleration of inflammatory reactions and adverse outcomes.<sup>59</sup> Meanwhile, HDL-C serves as an anti-inflammatory lipoprotein by binding and neutralizing bacterial lipopolysaccharides to facilitate their excretion.<sup>60</sup>



Lipoprotein-Z (LP-Z) is a recently identified free cholesterol-rich LDL-like lipoprotein with hepatotoxicity. Plasma LP-Z is undetectable in the general population. In contrast, a study found that LP-Z was remarkably detectable in 30.8% of pretransplant cirrhotic patients.<sup>61</sup> Furthermore, patients with cirrhosis exhibited low levels of circulating lecithincholesterol acyltransferase, which may account for the production of LP-Z. They also found that LP-Z was associated with a worse Child-Pugh class and a higher MELD score, rendering increased mortality in cirrhotic patients.

### Future directions

Despite the increasing interest in the investigation of lipids/lipoproteins in cirrhosis, targeting metabolic processing of these bioactive substances as a specific treatment has not been fully clarified. Moreover, it is pivotal to exploit the dynamic nature and mechanistic insights pertinent to the roles of individual lipids in the development and progression of cirrhosis. Further in-depth studies are necessary to dissect the mechanism of lipid metabolism and homeostasis in distinct stages within cirrhosis.

### Conclusions

In summary, we herein review the potential roles of serum lipids and lipoproteins in the development of cirrhosis and the prognosis of cirrhotic patients in addition to the underlying mechanisms regarding their expression abnormalities. The effects of serum lipids on cirrhosis as evidenced by the current studies are deciphered comprehensively. However, more efforts are still warranted to determine the clinical relevance of serum lipids/lipoproteins in the context of cirrhosis in order to develop risk stratification and therapeutic strategies.

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### Conflict of interest

CS has been an editorial board member of *Gene Expression* since August 2022. The authors have no other conflict of interests related to this publication.

### Author contributions

Study concept and design (BXC, WTY, GYG, and CS), analysis and interpretation of data (XFF, XYW, YYH, and SPW), drafting of the manuscript (BXC, JLL, and CS), and critical revision of the manuscript for important intellectual content (KJ and WTL). All authors have made a significant contribution to this study and have approved the final manuscript.

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