

Clinical Advances in Fibrosis Progression of Chronic Hepatitis B and C

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Abstract

Chronic liver diseases, such as chronic hepatitis B (CHB) and chronic hepatitis C (CHC), are characterized by the presence of liver fibrosis, which may ultimately lead to cirrhosis. The progression of fibrosis is associated with various factors. Here, we review recent advances in the study of factors related to the progression rate of CHB- and CHC-induced fibrosis. Identification of these factors and establishment of a scoring system for cirrhosis risk are particularly important for predicting cirrhosis development, planning individualized treatment, and preventing fibrosis progression.

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Introduction

Liver fibrosis is a common long-term pathological consequence of viral hepatitis, including chronic hepatitis B (CHB) and chronic hepatitis C (CHC).^{1,2} Due to continuous replacement of normal liver tissue with extracellular matrix (ECM), liver fibrosis results in progressive distortion of the normal hepatic architecture. These changes can evolve into cirrhosis. Severe complications of liver cirrhosis, including portal hypertension, ascites, varices, hepatic encephalopathy, hepatocellular carcinoma, hepatopulmonary syndrome, hepatorenal syndrome, and coagulation disorders, increase the risk of mortality in patients with chronic liver disease.³

The mechanisms underlying fibrogenesis in the liver have not been fully characterized. Accumulating evidence indicates that fibrosis can be triggered by continuous stimulation produced by infection with hepatitis B or C virus (HBV or HCV, respectively) through a three-step cascade.⁴ According to the

current model, the process begins with a preinflammatory stage (Step 1), during which hepatic stellate cells (HSCs) are activated directly through the paracrine action of cytokines released by necrotic hepatocytes. Subsequently (Step 2), preactivated HSCs are further stimulated by infiltrating leukocytes and platelets, as well as by activated Kupffer cells, hepatocytes, and sinusoidal endothelial cells, to transdifferentiate into proliferative, fibrogenic, and contractile myofibroblasts (MFBs). Lastly, in the postinflammatory stage (Step 3), cytokines are released and ECM components are produced by MFBs. During the postinflammatory stage, there is an imbalance of ECM production and degradation, which are controlled by regulation of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), respectively, resulting in an overabundance of ECM accumulation and, ultimately, the development of liver fibrosis (see Fig. 1).⁵

A variety of factors have been proposed to contribute to the progression of liver fibrogenesis, including host factors, viral factors, therapeutic strategies, and interactions with comorbid conditions (see Fig. 2). Here, we summarize recent advances in the characterization of factors related to fibrosis progression.

Host factors

Demographic features

The putative association between age at infection and fibrosis progression in CHB and CHC patients remains controversial. Age has been identified in a number of studies as an important factor that can predict the progression rate of fibrosis and the development of cirrhosis.⁶⁻¹⁰ For example, fibrosis progression was found to be relatively slow in CHC patients younger than 20 years old; fibrosis was found to accelerate with increased age, perhaps due to reduced immune defense.⁶ The natural history of chronic HBV infection also varies with age of infection. Compared with patients younger than 45 years old, the cumulative probability of cirrhosis development was significantly higher in patients older than 45.⁷ However, there are contradictory results in the literature as well.¹¹ Interestingly, donor age was also reported to be related to fibrosis progression in patients with recurrent HCV infection after liver transplantation.¹²

Advanced fibrosis is more common among male than female CHB patients.^{6,10,11} This gender difference might be explained, at least in part, by higher prevalence rates of drinking, smoking, and obesity in males. Additionally, it could be that female gender is protective against progression of liver fibrosis in CHC; it has been suggested that long-term exposure to estrogen may reduce liver fibrosis.¹³ In addition,

Keywords: Chronic hepatitis B; Chronic hepatitis C; Liver fibrosis; Disease progression.

Abbreviations: CRS, cirrhosis risk score; CHB, chronic hepatitis B; CHC, chronic hepatitis C; ECM, extracellular matrix; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSCs, hepatic stellate cells; IR, insulin resistance; MFBs, myofibroblasts; MMPs, metalloproteinases; REVEAL-HBV, Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus; TGF- β 1, transforming growth factor β 1; TIMPs, metalloproteinases.

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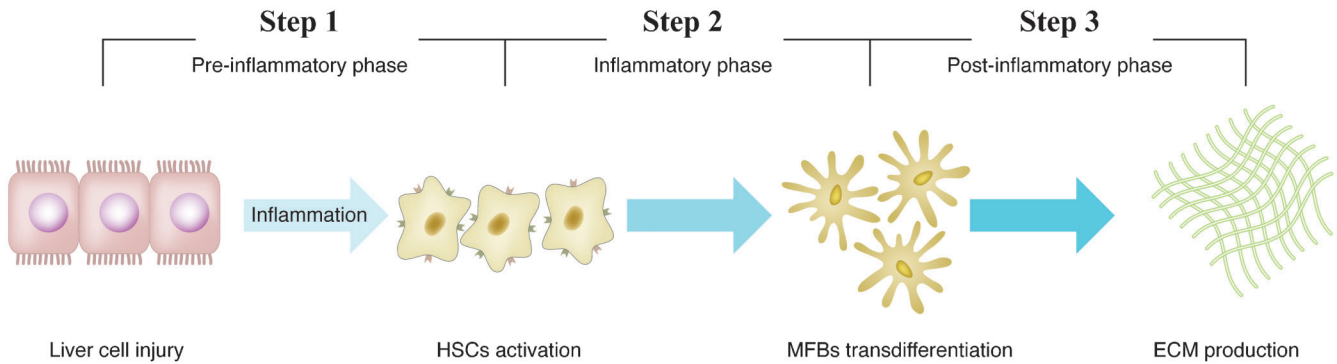


Fig. 1. Synopsis of pathogenetic mechanisms of liver fibrogenesis. HSCs: hepatic stellate cells; MFBs: myofibroblasts; ECM: extracellular matrix.

pregnancy may have a beneficial influence on the long-term progression of liver fibrosis, whereas menopause appears to be associated with accelerated fibrosis progression in female CHC patients.¹³

In summary, the current evidence indicates that both age and gender influence the progression of liver fibrosis. Specifically, older age and being male appear to be associated with faster progression of fibrosis.

Host genetic factors

The development of genotyping techniques and candidate gene approaches has enabled researchers to investigate the association between liver fibrosis progression and gene polymorphisms with known or supposed functions in pathways involved in fibrogenesis, inflammatory responses, oxidative stress, apoptosis, and necrosis.¹⁴ For example, Richardson *et al.* examined eight candidate genes and found that six of them, namely *HFE*, *MTP*, *APOE*, *CCR5*, *SOD2*, and *CTLA4*, were related to a more rapidly progressive fibrosis in CHC.¹⁵

Additionally, Boursier and Louvet found that the presence of the G/G genotype at a single nucleotide polymorphism (SNP) of interest in the transforming growth factor $\beta 1$ (*TGF- $\beta 1$*) gene was associated significantly with greater severity of fibrosis in CHC patients.¹⁶ Thus far, approximately 30 and 10 genes have been identified as being related to fibrosis progression in CHC and CHB, respectively (see Table 1).¹⁷

Although candidate gene techniques allow the genetic architecture of complex traits to be explored, the utility of this technique is limited greatly by its reliance on existing biological knowledge about presumed or known phenotypes.¹⁸ Genome-wide scanning, which can proceed without any presuppositions of the significance of specific phenotypes,¹⁸ has been widely applied in investigations of associations between genetic factors and multiple disease processes, including liver fibrosis. Huang *et al.* published a study that included 420 subjects with well-documented CHC and established fibrosis staging and revealed that among 23,823 SNPs, there was a group of seven SNPs that formed a cirrhosis risk score (CRS) signature that could identify

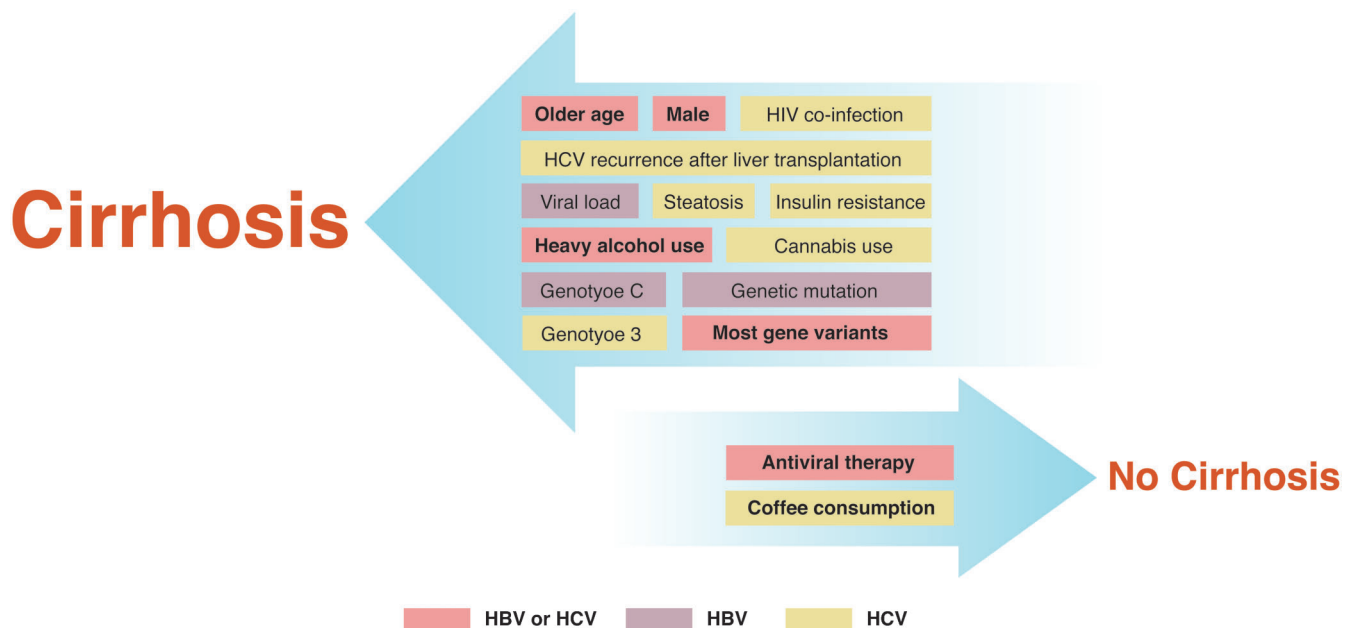


Fig. 2. Risk and protective factors of liver fibrosis progression in HBV and HCV infected patients. HBV: hepatitis B virus; HCV: hepatitis C virus.

Table 1. Chronic hepatitis C or B-induced fibrosis - associated genes identified by candidate gene studies or genome - wide association studies

	Candidate gene studies	GWAS
Chronic hepatitis C	Angiotensinogen, ApoE, C5a, CCR5, CPT1A, CTLA4, CYP2D6, DDX5, epoxide hydrolase, HFE, HLA II, IL1E, IL6, IL10, IL12, IFN γ , MCP-1, MMP-1, MMP-3, MMP-9, MTP, MX-1, OAS-1, PAR-1, PKR, SLC11A1, SOD2, TAP2, TGFE1, TNF	AP3S2, AQP2, AZIN1, DEGS1, STXBP5L, TLR4, TRPM5
Chronic hepatitis B	Angiotensinogen, CD24, COL1A1, CXCL10, GSTP1, IL10, MBL, TNF-, TNF-, vitD-rec	/

GWAS: genome-wide association studies.

Caucasian CHC patients at high risk of cirrhosis (also see table 1).¹⁰ The CRS has since been validated in two independent longitudinal trials.^{11,19}

Viral factors

Viral genotypes

Viral genotype has been implicated in the clinical outcome of chronic viral hepatitis. However, the potential association between particular viral genotypes and the progression of liver fibrosis in CHC patients remains controversial. Probst *et al.* conducted a systematic review and meta-analysis to investigate this issue. When they examined single-biopsy studies, they found a potential association between HCV genotype 3 and rapid progression of fibrosis.²⁰ This putative association, however, did not hold in paired-biopsy studies, suggesting that the single-biopsy analysis may have suffered from indication bias related to a short observation period and small sample size.²⁰

Ten HBV genotypes (labeled A–J) with differing geographical and ethnic distribution patterns have been identified.²¹ Liu and Kao found that HBV genotypes B and C occur in Asian populations with greater frequency than other genotypes, and that genotype C was associated with an elevated risk of liver cirrhosis.²² In contrast, Yuen *et al.* observed that patients with HBV genotype C had delayed hepatitis B e antigen (HBeAg) seroconversion, worse liver biochemistry, prolonged active HBV DNA proliferation, and higher hepatitis viral loads across different phases of the disease's natural course relative to genotype B patients. There was no significant difference between genotype C and B patients in their probability of developing cirrhosis-related complications.^{23,24} It should also be noted that the prevalence rate of the combination of preS deletions and A1762T/G1764A mutations was relatively higher in patients infected with genotype B than genotype C,^{22,25} which may explain in part the worse clinical outcomes observed among genotype C patients in the study by Liu and Kao. HBV genetic mutations are associated with increased risk of liver cirrhosis. The precore G1896A mutant and the basal core promoter A1762T/G1764A dual mutant have been linked to greater risk of cirrhosis in HBV carriers.^{26,27} Moreover, the preS deletion mutant appears to be an independent predictor of liver cirrhosis.^{21,25}

Viral load

A Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study was carried out in Taiwan with 3,582 untreated HBV carriers. During the 11-year follow-up period, they found that serum

HBV-DNA level correlated positively with the incidence of cirrhosis. Among 365 newly diagnosed cirrhosis patients, the cumulative incidence of cirrhosis in those with serum HBV-DNA levels <300 copies/mL at baseline was significantly lower than that in those with levels >10⁶ copies/mL at baseline.²⁸ Increasing serum HBV-DNA level has been proposed as an independent risk predictor for fibrosis progression and cirrhosis.²⁶ Presumably, high HBV-DNA load might lead to more severe liver damage during the immune clearance phase and, therefore, accelerate the progression of fibrosis.^{26,28}

As for HCV, preexisting evidence of the association between serum HCV RNA levels and liver fibrosis is limited and conflicting. Some studies showed no significant correlation,^{29–31} while other researchers reported significant relevance of serum HCV RNA level and fibrosis.^{32–34} Rarely are longitudinal studies regarding fibrosis progression rate are found, and further related studies remain to be conducted.

Therapeutic strategies

Anti-HCV therapy

The standard therapeutic strategy for patients with CHC is combined administration of standard or pegylated interferon- α (IFN- α) with ribavirin. The addition of polyethylene glycol to IFN- α , through a process known as pegylation, prolongs the half-life of IFN- α . The primary goal of anti-HCV therapy is a sustained virological response (SVR), defined as undetectable HCV RNA levels 24 weeks after completion of the treatment.³⁵ A cohort of 150 American patients with SVRs after anti-CHC therapy was followed for 5 years.³⁶ In the fourth year, 82% of patients exhibited a lower fibrosis score than they had prior to initiating therapy.³⁶ Similar results were obtained from other researchers.³⁷ These findings indicated that SVR following IFN- α plus ribavirin therapy could benefit and improve outcome in patients with advanced liver fibrosis. Although IFN- α plus ribavirin therapy has been applied widely, numerous adverse events have been reported. Hence, there is a sustained interest in IFN-free regimens, such as sofosbuvir.³⁸ However, the efficacy of IFN-free regimens for preventing fibrosis progression remains to be elucidated. It is important to note that SVR rate varied by different HCV genotypes. Specifically, the SVR rate was approximately 40–50% in the patients with HCV genotype 1 and 80% in those with genotype 2 and 3.³⁹

Anti-HBV therapy

The main goals of anti-HBV therapy are to prevent disease progression to cirrhotic endpoints and to improve survival by

suppressing HBV DNA replication, ideally achieving a sustained reduction of HBV DNA to undetectable levels.⁴⁰ There are two categories of regimens licensed for the treatment of CHB, namely standard or pegylated IFN- α and five nucleoside/nucleotide analogues (NAs).⁴¹ Independent follow-up studies showed that IFN therapy retarded the progression of fibrosis and reduced progression to cirrhosis in HBeAg-positive patients.^{42,43} A meta-analysis conducted in 2010 indicated that IFN- α treatment can reduce the risks of overall hepatic events and of cirrhotic complications, particularly among treatment responders.⁴⁴ Meanwhile, long-term NA-based therapy with third-generation NAs (entecavir or tenofovir) has been reported to reverse fibrosis, and even cirrhosis, in several registered clinical trials.⁴⁵⁻⁴⁹

Comorbidities

Human immunodeficiency virus infection

Emerging lines of evidence suggest that human immunodeficiency virus (HIV) infection accelerates fibrosis progression in HCV patients.⁵⁰ Without successful treatment, more than 20% of HIV/HCV coinfecting patients with null or mild fibrosis progressed to advanced fibrosis within 5 years.⁵¹ Pegylated IFN- α plus ribavirin therapy has been reported to reduce the incidence of liver complications and death in HIV/HCV coinfecting patients.⁵² The molecular mechanisms involved with rapid fibrosis progression in coinfecting patients are complicated, but the most relevant mechanisms involved viral factors, immune system, fibrinogenetic/inflammatory mediators, and metabolic alteration. This topic was recently reviewed in detail by Mastroianni *et al*.⁵³

Hepatic steatosis

The strong association between HCV-related steatosis and fibrosis progression has been demonstrated in multiple cross-sectional or prospective studies, previously reviewed by Lonardo *et al*.⁵⁴ The most convincing evidence among these studies comes from the meta-analysis conducted by Leandro *et al*.⁵⁵ The study included 3,068 CHC patients from 10 centers in Europe, Australia, and North America and showed that steatosis was a risk factor for fibrosis progression. In addition, based on the results of its subgroup analyses, the association between steatosis and fibrosis was reasonably inferred to be mediated by hepatic inflammation. However, another meta-analysis indicated that the frequency of hepatic steatosis in CHB patients was similar to that in the general population, suggesting that hepatic steatosis may be related to metabolic factors, rather than fibrosis stage, in CHB patients.⁵⁶

Insulin resistance

Insulin resistance (IR), a major cause of type 2 diabetes, was shown to drive fibrosis progression in studies conducted by two independent research groups.^{57,58} Subsequent experimental studies revealed that CHC patients with IR were prone to elevations in serum leptin and TNF- levels, which may promote the activation of HSCs and, consequently, enhance fibrosis progression.⁵⁹ Another study showed insulin resistance might directly impact HSCs and raise connective tissue growth factor levels, leading to excessive generation of ECM.⁶⁰ Alternatively, IR-induced hepatic lipid accumulation

may increase oxidative stress, thereby promoting fibrosis progression.⁶¹ However, IR does not appear to be associated with fibrosis severity in CHB patients.^{62,63}

Other factors

Alcohol intake

The potential association between alcohol consumption and fibrosis progression in HCV-infected patients is still under debate. In a majority of studies, it has been shown that heavy alcohol use (>50 g/day) exerted an adverse effect on fibrosis progression.^{6,64,65} However, the data regarding light or moderate alcohol use have been conflicting.⁶⁶ The reason for this discrepancy is unclear, but may be due to patients altering their alcohol habits as a consequence of their disease awareness.

Coffee consumption

Epidemiological studies have shown that coffee drinking was associated with a decreased prevalence of cirrhosis in patients with chronic liver disease.⁶⁷ Regular coffee consumption is known to have hepatoprotective benefits in CHC patients; advanced fibrosis has been observed less often in patients who drink coffee than in patients who do not.^{68,69} It has been speculated that coffee might prevent fibrosis progression by regulating insulin sensitivity, leading to alleviation of inflammation and reduction of oxidative stress. Conversely, no significant benefits of regular tea intake were found in CHC patients.⁶⁹ There has been only one report evaluating the link between coffee consumption and fibrosis in CHB patients, and no benefit was identified as measured by transient elastography.⁷⁰ Further confirmation of the association is needed.

Recurrent HCV after liver transplantation

CHC is a principal indication for liver transplantation. Approximately 30% of patients who receive a liver transplant go on to develop severe fibrosis within 5 years due to HCV recurrence.^{71,72} The progression of fibrosis following transplantation appears to be nonlinear over time. Walter *et al*. observed rapid elevation of fibrosis during the first 3 years after transplantation, followed by less rapid progression in the subsequent 2 years.¹² Rapid fibrosis progression in the initial period following transplantation might be related to preoperative antiviral therapy, immunosuppressive regimens, short-term use of hormones, and donor age. Interestingly, a retrospective, single-center study showed that sirolimus-based immunosuppression reduced the risk of fibrosis for HCV infection after liver transplantation.⁷³

Cannabis use

Since daily cannabis smoking may be a predictor of fibrosis progression in CHC patients,^{74,75} reduction or discontinuation of cannabis use is recommended for HCV-infected patients. The cannabinoid receptors CB1 and CB2 have been implicated in the fibrogenic influence of cannabis. Inactivation of CB1 receptors by genetic or pharmacological approaches prevented fibrogenesis through downregulation of TGF- β 1 levels and reduction of fibrogenic cell accumulation.⁷⁶ In addition, CB2 knockout mice chronically exposed to carbon-tetrachloride

demonstrated facilitated apoptosis and reduced proliferation of hepatic MFBs relative to wild-type controls.⁷⁷

Conclusions

Significant progress has been achieved in the analysis of relevant factors affecting progression of CHB- and CHC-induced fibrosis. Multiple factors, including host factors, viral factors, therapeutic strategies, and comorbidities, are involved in the progression of fibrosis, and the molecular mechanisms underlying these influences have been partially elucidated. Meanwhile, researchers continue to examine how single or multiple factors contribute to the risk of cirrhosis development in patients with chronic viral hepatitis,^{10,15,26} which, nevertheless, remains to be validated in large samples from different populations. Prospectively, the identification of new predictors and the establishment of a risk score system remain clinical challenges in the assessment of risk of cirrhosis development and the prediction of clinical outcomes in CHB and CHC patients. Continued progress in these areas is critical because individual risk profiles play a critical role in therapeutic strategy determination and prognostic judgment.

Conflict of interest

None

Author contributions

Writing the manuscript and performing literature searches (YJW). Editing and revising the manuscript (MYX, LGL).

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