

# World Journal of *Clinical Cases*

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## Effects of alcohol consumption on viral hepatitis B and C

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### Abstract

The liver is the main target organ for hepatitis viruses and the vital organ for alcohol metabolism. These two factors of viral hepatitis and alcohol abuse in combination can exert dual harmful actions, leading to enhanced damage to the liver. Epidemiological studies have revealed a higher prevalence of hepatitis C virus (HCV) infection among alcoholics than the general population. The interaction of alcohol with viral hepatitis [e.g., hepatitis B virus (HBV), HCV] and the underlying mechanisms are not fully understood. The effects of alcohol on viral hepatitis include promoted viral replication, weakened immune response, and increased oxidative stress. Clinically, alcohol abuse is correlated with an increased risk of developing end-stage liver cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis B and C, suggesting that the combination of alcohol and HBV/HCV lead to more severe liver damage. The influence of mild to moderate alcohol drinking on the HBV-induced liver fibrosis, cirrhosis, and hepatocellular carcinoma among patients infected with HBV remains unclear. Unlike HBV infected patients, no safe level of alcohol intake has been established for patients with HCV. Even light to moderate alcohol use can exert a synergistic effect with viral hepatitis, leading to the rapid progression of liver disease. Furthermore, interferon-based therapy is less effective in alcohol drinkers than in control patients, even after abstinence from alcohol for a period of time. Therefore, abstaining from alcohol is highly recommended to protect the liver, especially in individuals with HBV/HCV infection, to improve the clinical efficacy of antiviral treatment and prevent the rapid progression of chronic viral hepatitis.

**Key Words:** Alcohol; Hepatitis B virus; Hepatitis C virus; Viral hepatitis

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**Core Tip:** (1) Alcohol adversely affects hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in the liver *via* promoting viral replication, increasing oxidative stress, suppressing the viral immune responses, *etc.*; (2) The interaction of alcohol with viral hepatitis contributes to an increased risk of developing HBV- or HCV-induced liver fibrosis, end-stage cirrhosis, and even deadly liver cancer; and (3) Individuals with HBV or HCV infection should abstain from alcohol to slow the disease progression.

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## INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the two most common types of viral infections in the liver, with approximately 257 million and 71 individuals living with HBV and HCV worldwide, respectively, and as many as 780000 HBV- and 400000 HCV-related deaths annually[1-3]. Epidemiologic studies suggest that approximately 10% to 15% of patients with HCV infection are coinfecting with HBV[4]. HBV infection is particularly prevalent in China, and HBV-related deaths account for 63% of deaths from liver cirrhosis and other chronic liver diseases, and 53% of deaths from liver cancer[5]. Alcohol abuse is among the high-risk factors contributing to the accelerated progression of chronic hepatitis B (CHB) and chronic hepatitis C (CHC) into more severe liver diseases such as liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC)[6-8].

Alcohol consumption is very common across different cultures and religions worldwide. Indeed, in 2016, as high as 57% of the population aged 15 and older consumed alcohol. The use and misuse of alcohol are leading risk factors for a broad spectrum of health problems worldwide, directly influencing health-associated targets of the sustainable development goals including those for infectious diseases (viral hepatitis, human immunodeficiency, tuberculosis), maternal and child health, mental health, noncommunicable diseases, injuries, and poisonings.

Alcohol is mainly metabolized and converted into more toxic acetaldehyde in the liver. Combined alcohol abuse and viral hepatitis may lead to more severe hepatic damage. To date, the mechanisms underlying the interaction of alcohol with viral hepatitis (*e.g.*, HBV, HCV) are not fully understood. In addition, the effects of alcohol intake on the progression of HBV- or HCV-associated liver disease have not been accurately examined.

Herein, we performed a literature review and synthesized existing studies on the complex interaction of alcohol with HBV and HCV infections.

## PREVALENCE OF HBV/HCV INFECTION AND ALCOHOL CONSUMPTION

Excessive alcohol use is related to an increased risk of spreading the infection of viruses, including HBV and HCV[9]. In fact, HCV infection is more prevalent in patients with alcohol use disorders (AUDs) than the general population. CHC is associated with excessive current and previous alcohol drinking[10]. The World Health Organization HCV elimination strategy also highlights the requirement for addressing alcohol intake as a co-morbidity among patients with HCV infection[11]. The prevalence of hepatitis C varies ranges from 4.6% to 55.5% in alcoholics[12-18]. A systematic review of 133 publications showed that the prevalence of HCV infection is up to 30-fold higher in alcoholics compared with the general population[18]. Meanwhile, alcohol abuse is more prevalent in patients with HCV infection who also have a longer duration of alcohol use than the general population. A systematic review of 11 previous studies including 286641 patients with CHC reported that 22.3% of the patients identified with AUDs, a much greater proportion than the general population [19]. A previous international study showed that 28%, 32%, and 50% of HCV patients with decompensated cirrhosis had AUD in British Columbia, New South Wales, and



Scotland, respectively[20]. Rosman *et al*[21] reported that anti-HCV is significantly more prevalent in alcoholics than non-drinkers, indicting alcohol misuse as an independent risk factor associated with HCV infection. Although direct evidence is lacking, it has been postulated that alcohol use enhances the acquisition of HCV after exposure to the virus[22,23].

Unlike the relatively high incidence of HCV infection in alcohol drinkers, the prevalence of HBV infection in this population is still inconclusive. Some previous studies have revealed a higher frequency of HBV markers in the serum of chronic alcoholics[24-26] as well as of patients with alcoholic hepatitis and liver cirrhosis[27] compared with the general population. A study from Taiwan reported a link of alcohol drinking with a lower prevalence of hepatitis B surface antigen (HBsAg)[28], which is not consistent with the study by Rosman *et al*[21], indicating that the prevalence of anti-HCV is significantly greater in alcoholics than in non-drinkers, whereas there is no significant difference in the prevalence of HBV between alcohol drinkers and non-drinkers. These previous findings suggest that alcohol abuse is an independent risk factor for HCV but not HBV infection[21], but the reason for the difference remains unclear. Lin *et al*[29] proposed that HBV infection can play an important role in the evolution of the aldehyde dehydrogenase 2 (ALDH2\*2) allele in the Chinese Han population. Geographical areas with a particularly high prevalence of HBV infection are located in Eastern Asia, especially in China. In addition, 30%-40% of Asian populations are deficient in ALDH2, a key enzyme in detoxifying the ethanol metabolite acetaldehyde. Variation in the ALDH gene influences drinking behavior and the risk of alcoholism development through acetaldehyde formation. In the long-term HBV endemic in China, non-alcohol drinking HBV carriers may have evolutionary advantages over alcohol-drinking HBV carriers. Accordingly, HBV carriers who do not drink or drink in moderation may have better chances of surviving than those who drink more alcohol. It has also been hypothesized that the ALDH2\*2 allele, through the natural selection of liver diseases, becomes the adaptive gene among Chinese Han population, resulting in a better chance of surviving and facilitating transmission of the virus to the next generation. In summary, HBV selects ALDH gene mutations, which can affect drinking behavior, making HBV-infected people not good at drinking alcohol, and providing more opportunities for long-term survival and transmission of HBV.

## INTERACTION OF ALCOHOL WITH HEPATITIS VIRUS AND THE UNDERLYING MOLECULAR MECHANISMS

Both alcohol and HBV/HCV infection are associated with liver injury, and the interactions of alcohol with hepatitis B and C infections are complex. Although the exact underlying mechanisms are not fully understood, studies have provided evidence that alcohol can increase the replication of HBV/HCV, oxidative stress, and cytotoxicity but decrease antiviral immune responses in the liver[30].

### ***Alcohol enhances the replication of HBV and possibly HCV***

Existing *in vitro* and *in vivo* studies have shown that alcohol intake can increase the replication of HBV, and possibly HCV, as well their host hepatocytes. Larkin *et al*[31] found that the serum viral DNA load and levels of HBsAg increased by nearly 6-fold in mice treated with alcohol compared with those given the control diet. In the same study, elevated levels of HBV-RNA as well as surface, core, and X antigens were also observed after alcohol treatment, especially in the pericentral regions of the liver in mice. In *in vitro* studies, Ganesan *et al*[32] reported that the levels of HBV RNA, covalently closed circular DNA, and HBsAg were increased in response to alcohol treatment in HepG2.2.15 cells. Recently, Lin *et al*[29] showed that hepatitis B viral load was higher in alcoholic than non-alcoholic HBV patients. Alcohol can promote HBV transcription by regulating some key factors [*e.g.*, peroxisome proliferator-activated receptor alpha, farnesoid-X-receptor alpha, cytochrome P450 2E1 (CYP2E1)] as well as the hypoxia-inducible factor-1 $\alpha$ -dependent pathway, which have been proposed as potential molecular mechanisms whereby excessive alcohol consumption increases the replication of HBV in the liver[33-35]. In addition to the direct effect of alcohol on the replication of HBV, alcohol can act on lipid rafts with pivotal roles in viral entry and other processes of the viral life cycle, leading to indirect effects on HBV replication[23].

Unlike HBV, the effect of alcohol on the replication of HCV remains a subject of debate due to conflicting results from different studies. Ran *et al*[36] showed that alcohol treatment promoted HCV replication in Huh7 cells. Sobhanimonfared *et al*[37]

showed that acute alcohol treatment was associated with increased HCV replication, while chronic alcohol treatment led to decreased HCV replication in Huh 7 cells. By contrast, Plumlee *et al*[38] found that high concentrations of acute alcohol inhibited HCV replication in cell culture. Cromie *et al*[39] showed that even a small amount of alcohol can lead to an increase in serum HCV RNA in patients with HCV infection. In a meta-analysis, conclusive results were not reached regarding the effect of alcohol consumption on serum HCV-RNA levels[40].

### ***Alcohol suppresses antiviral immune responses***

In the cases of HBV and HCV infections, eliciting antiviral immune responses, including innate and adaptive immune responses, are important host defenses in the control of viruses. Excessive alcohol intake adversely affects the antiviral immune system in response to hepatitis viruses, leading to unfavorable outcomes of HBV or HCV infection. In terms of innate immune responses, alcohol exerts inhibitory effects on the antiviral activity of natural killer cells. In addition, long-term alcohol consumption appears to affect innate immune responses to hepatitis virus infection in the production of some important cytokines including interferon (IFN)- $\alpha$ , IFN- $\gamma$ , tumor necrosis factor- $\alpha$ , transforming growth factor  $\beta$ , and interleukin 10[41-45]. In the adaptive immune responses to hepatitis viruses, alcohol reduces the number of B cells, particularly circulating B cells[46-48]. Alcohol may suppress the adaptive immune response of B cells by reducing the number of B cells, subsequently decreasing the production of antibodies against HBV antigens, thereby leading to persistent HBV infection and development of CHB. Data from animal and human studies have clearly shown that alcohol reduces the number of T cells, alters their patterns, suppresses their activation, and promotes the apoptosis of T cells[49]. Alcohol has also been shown to affect dendritic cells, which are critically important immune cells in adaptive immune responses to virus infection in patients with HCV infection[50,51].

### ***Alcohol intake increases oxidative stress in the liver***

Chronic alcohol intake induces the microsomal ethanol-oxidizing system, including that of CYP450. Among the variants of CYP450, CYP2E1 is markedly affected by chronic alcohol consumption, with activity that increases in response to alcohol. Free radicals (*e.g.*, superoxide, hydroxyl radicals, hydrogen peroxide) are generated in ethanol metabolic pathways involving CYP2E1, and excessive oxygen radicals cause oxidative stress. Rigamonti *et al*[52] showed that moderate alcohol consumption (< 50 g/d) and heavy alcohol drinking (> 50 g/d) increase the risk of developing oxidative stress 3-fold and up to 24-fold, respectively. Oxidative stress can activate nuclear factor kappa B[53], playing a key role in hepatic inflammation, liver injury and regeneration, and the development of HCC[54-56]. Moreover, CYP2E1-associated oxidative stress increases the ethanol-induced transactivation of HBV[57].

Oxidative stress is a negative effect exerted by reactive oxygen species, highly reactive oxygen intermediates that can chemically modify the structure of various molecules and thus pose a threat to the living cell. High levels of reactive oxygen species induce oxidative DNA damage, such as 8-hydroxy-2-deoxyguanosine (8-OHdG), an important biomarker for oxidative stress. Wong *et al*[58] showed that HBV- and HCV-induced hepatic inflammation and alcohol consumption can induce oxidative stress, with alcohol consumption correlated with 8-OHdG. The accumulation of 8-OHdG associated with alcohol in hepatocytes may establish a possible link between HBV infection and hepatic carcinogenesis[59]. These findings provide an explanation for the enhanced progression of disease in hepatitis patients with alcohol abuse.

In addition, the interaction of alcohol with hepatitis virus may involve activation of the unfolded protein response[60], promotion of hepatic steatosis[61], increase in iron storage[62,63], and induction of hepatocytes apoptosis[64-66]. Moreover, in the progression of liver disease, these mechanisms can interact with each other. For example, higher levels of oxidative stress affect innate immunity, resulting in the more rapid spread of the virus and progression to end-stage liver disease.

## **EFFECTS OF ALCOHOL DRINKING ON THE PROGRESSION OF HBV OR HCV ASSOCIATED LIVER DISEASE**

Alcohol intake has a synergistic effect with viral hepatitis on the liver disease progression. For example, a case control study found synergism between positive

HBsAg or HCV RNA and heavy alcohol drinking[67]. Among patients coinfecting with HBV and/or HCV, alcoholic patients tended to be younger and had a higher male-to-female ratio, worse performance status, more severe liver cirrhosis, more advanced cancer stage, and higher tumor burden compared to non-alcoholic patients[68]. In terms of HCC, the values of multivariate odd ratios (ORs) [95% confidence intervals (CIs)] were 15.3 (4.3-54.4), 12.6 (2.5-63.1), 4.5 (1.4-14.8), and 4.3 (1.9-9.9) for anti-HCV, HBsAg, heavy alcohol intake (> 80 mL ethanol per day), and diabetes mellitus, respectively. There were synergistic interactions between heavy alcohol intake and chronic viral hepatitis (OR: 53.9, 95%CI: 7.0-415.7)[69].

### Effects of alcohol on the progression of HBV-associated liver disease

A study of 1113 Japanese patients with CHB revealed that the prevalence of hepatitis B e antigen (HBeAg) tended to be higher and decrease more slowly with age in heavy drinkers (> 60 g alcohol per day) than in nondrinkers, indicating that alcohol misuse may delay the loss of HBeAg[70]. Other studies in the Japanese population found that alcohol intake, particularly excessive alcohol intake (> 60 g alcohol per day), can increase viral inflammatory changes in the liver in patients with persistent HBs-antigenemia[71] or HBsAg carriers[72]. Li *et al*[65] documented that interactions of alcohol and HB synergistically promote high-fat diet-induced hepatic steatosis in mice. The same study showed that alcohol consumption is associated with an increased risk of developing hepatic steatosis in HBV-infected patients.

Alcohol abuse in patients with CHB is correlated with an elevated risk of developing liver cirrhosis and HCC. In agreement with the above findings, Lin *et al*[73] indicated that heavy alcohol consumption significantly increased the risk of HCC in patients with HBV-related liver cirrhosis. It was also shown that HCC occurred in 28.8%, 15.8%, and 10.4%, respectively, in cirrhotic patients with HBV infection and alcoholism, cirrhotic patients with HBV infection, and cirrhotic patients with alcoholism. In addition, the 10-year cumulative incidences of HCC were 52.8%, 39.8%, and 25.6%, respectively, and the annual incidences of HCC were 9.9%, 4.1%, and 2.1%, respectively, in cirrhotic patients with HBV infection and alcoholism, cirrhotic patients with HBV infection, and cirrhotic patients with alcoholism[73]. Notably, these incidences were significantly greater in cirrhotic patients with HBV infection and alcoholism than in those in patients with HBV infection or alcoholism alone[73]. Heavy alcohol consumption accelerates the progression of liver disease into liver cirrhosis and eventually into HCC with a 1.3- to 8.4-fold increased risk[74]. A longitudinal study of healthy blood donors with positive HBsAg in Japanese population spanning the period between 1972 and 1975 demonstrated that alcohol intake > 27 g/d was associated with more than a 5-fold increase in the relative risk (RR) of developing HCC[75]. A prospective cohort study of 610 patients with consecutive positive HBsAg noted that cumulative alcohol intake of 500 kg and more was significantly associated with the rate of carcinogenesis, with a RR (95%CI) of 8.37 (2.70-25.93,  $P = 0.0002$ )[76]. In addition, alcohol intake was reported to affect the mortality of HBV-related liver disease in a study by Ribes *et al*[77], in which 2352 HBsAg-positive patients were followed up for 20 years, and lifetime chronic consumption of alcohol more than 60 g/d was associated with a 6-fold increase in the risk of death from liver cirrhosis and HCC. Moreover, patients with HCC caused by CHB and chronic alcohol consumption are approximately 10 years younger than patients with HCC caused by CHB alone[78, 79], suggesting that heavy alcohol drinking increases both the mobility and mortality of HCC in CHB patients.

It is worth noting that, compared with heavy alcohol drinking, the influence of mild to moderate alcohol drinking on HBV-induced liver fibrosis, cirrhosis, and HCC among patients infected with HBV remains unclear. A cross-sectional study of CHB patients showed that the incidence of advanced liver fibrosis in those patients who reported drinking alcohol (1-20 g alcohol per day) was similar to that in those who abstained from alcohol[80]; hence, alcohol consumption should be kept to a minimum in patients with HBV infection[81]. A study of 1045 hepatitis B patients showed that the prevalence of advanced liver fibrosis among patients with mild to moderate alcohol intake (26, 18.8%) was comparable to that of non-drinkers (190, 21.0%) ( $P = 0.57$ )[80]. The large-scale, prospective cohort REVEAL-HBV study of more than 3500 patients (aged 30-65 years) in Taiwan showed that male sex, older age, seropositivity for HBeAg, and habitual alcohol consumption are significantly correlated with the development of HCC[82]. Taken together, these studies suggest that light-to-moderate habitual alcohol consumption appears to have, at best, a modest correlation with the progression of HBV-induced liver disease[74]; this effect was not always significant, particularly in studies with a relatively small sample size. In addition, more accurate epidemiological and pathophysiological data obtained from larger cohort studies are

required in order to examine and trace the risk of developing liver cirrhosis and HCC in patients with HBV infection and light-to moderate alcohol intake.

### **Effects of alcohol on the progression of HCV-induced liver disease**

Alcohol intake is an independent risk factor associated with the progression of HCV infection and its related liver disease[83,84]. Multiple lines of evidence have shown worsened outcome of patients with chronic HCV and heavy alcohol use, although the definition of heavy alcohol use is somewhat different. For example, alcohol intake (40 g ethanol per day or more) is associated with the more rapid progression of HCV-induced liver diseases, including HCV-induced liver fibrosis and cirrhosis, compared to patients who consumed lower levels of alcohol[85]. A meta-analysis showed that the RR of progression to liver cirrhosis was 2.33-fold (95%CI: 1.67-3.26) in patients with heavy alcohol intake (240-560 g per week) compared to those with less heavy alcohol intake among patients with chronic HCV infection[86]. Decompensated cirrhosis in patients with hepatitis C is independently correlated with AUD in British Columbia [hazard ratio (HR): 1.92, 95%CI: 1.76-2.10], New South Wales (HR: 3.68, 95%CI: 3.38-4.00), and Scotland (HR: 3.88, 95%CI: 3.42-4.40)[20]. Heavy alcohol intake increases the risk of HCC in patients with HCV infection[87,88]. Studies from Japan noted an increased risk of developing HCC in HCV patients who drank more than 65 g alcohol daily for over 5 years (RR: 3.04, 95%CI: 1.31-7.09)[89,90]. Similar to the findings in HBV-infected patients, heavy alcohol abuse is associated with an increased risk of developing HCC at a younger age in patients with HCV infection. Among HCV-positive patients who reported drinking alcohol (> 46 g/d), HCC occurred in patients at an average of  $26 \pm 6$  years, younger than  $31 \pm 9$  years for those who consumed alcohol less than 46 g/d[91]. Moreover, comparative analysis of tumor characteristics of HCC patients revealed that the tumors of heavy alcohol drinkers were significantly more anaplastic (5% with well-differentiated HCC *vs* 45% of nondrinkers) with increased extracapsular, capsular, and portal vein invasion and intrahepatic metastases[89].

Compared with heavy alcohol drinking, light-to-moderate alcohol intake has also been shown to promote the progression of HCV-related liver disease[92-94]. Monto *et al*[92] showed the incremental effects of alcohol on liver fibrosis. Although the liver fibrosis was overall more severe in HCV patients who drank heavily than in those who did not drink, there was a range of disease in each category of alcohol intake (light, moderate, and heavy). Another study of 1574 patients with hepatitis C and alcohol consumption was assessed in three groups of patients: No alcohol intake, moderate alcohol intake (0-49 g/d), and heavy alcohol intake (50 g/d or more). As a result, the rate of progression of fibrosis in fibrosis units per year increased from 0.125 (95%CI: 0.111-0.143) in the no alcohol intake group, to 0.143 (95%CI: 0.118-0.160) in the moderate alcohol intake group, and to 0.167 (95%CI: 0.133-0.174) in the heavy alcohol intake group[95]. In addition, there was a synergistic effect of HCV infection and the consumption of alcohol (< 40 g/d) with the development of HCC[96]. A prospective study showed that light-to-moderate alcohol intake (median alcohol intake: 15 g/d) increases the risk of developing HCC in patients with HCV-related liver cirrhosis (HR for alcohol consumption: 3.43, 95%CI: 1.49-7.92,  $P = 0.004$ )[97].

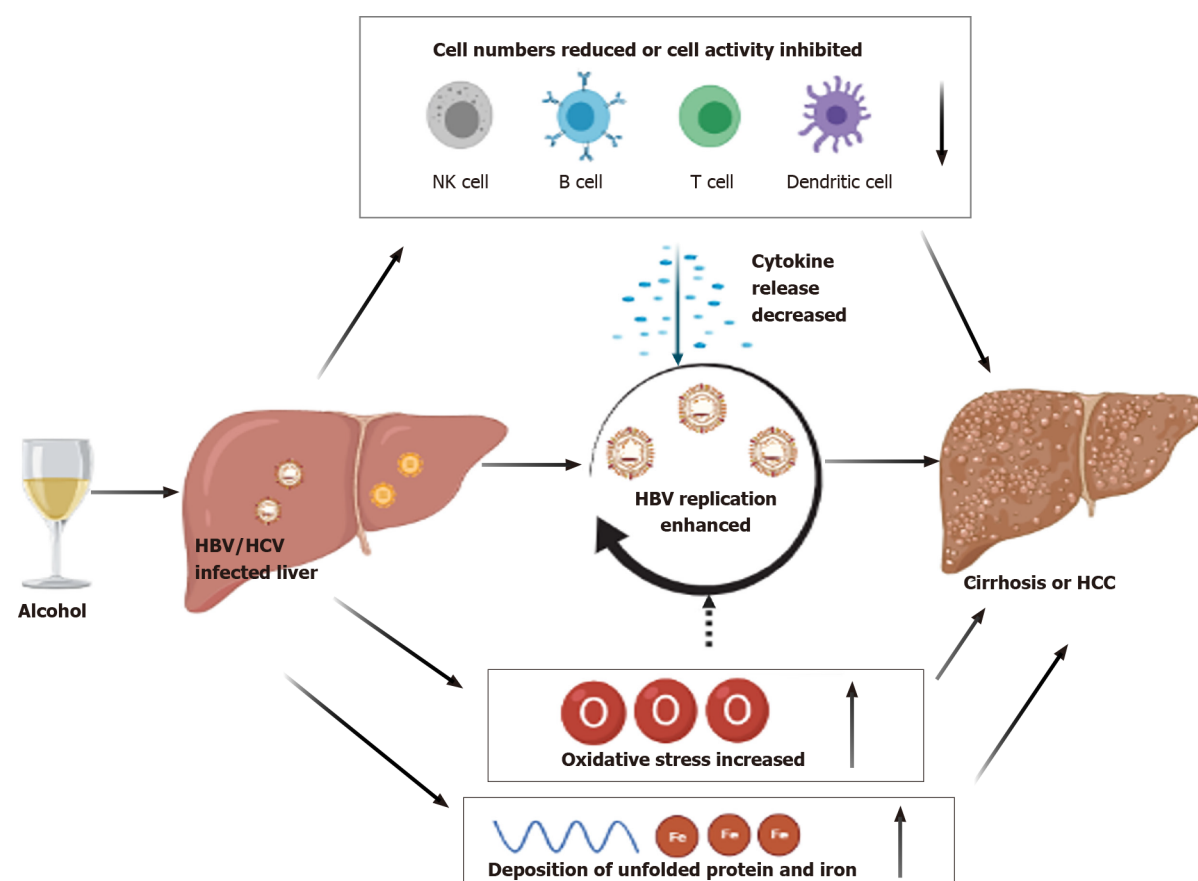
In summary, no safe level of alcohol intake has been established for patients with HCV. Even light-to-moderate alcohol use can exert a synergistic effect with viral hepatitis, leading to the rapid progression of liver disease.

## **EFFECTS OF ALCOHOL ON CLINICAL EFFICACY OF ANTIVIRAL TREATMENT OF HBV/HCV INFECTION**

IFN-based therapy is less effective in alcohol drinkers than in control patients, even after abstinence from alcohol for a period of time. As such, it has been recommended that patients with chronic infection of HCV should restrict alcohol intake to < 10 g/d, and abstinence from alcohol should be encouraged in patients with presence of liver cirrhosis or prior to IFN therapy[98]. Direct-acting antivirals are highly effective for the treatment of HCV infection, and alcohol intake is unlikely to alter achievement of sustained virologic suppression among patients with direct-acting antivirals treatment [99].

In terms of effects of alcohol drinking on the clinical efficacy of anti-HBV treatment, relative studies are limited. Hosaka *et al*[100] showed that alcohol consumption (> 200 kg) is a risk factor for cumulative HCC incidence rates at 5 years in patients with CHB treated with entecavir (HR = 2.21, 95%CI: 1.18-4.16,  $P = 0.013$ ).





**Figure 1** Effects of alcohol use on chronic hepatitis B or C. HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; NK: Natural killer.

In addition to the effects of alcohol intake on antiviral therapy, liver fibrosis, cirrhosis, and liver cancer, it has not been reported whether it can cause chronic acute liver failure and whether other pathogens could be involved in chronic hepatitis patients. At the same time, there is no detailed report on whether other related decompensation complications can occur more easily or earlier in patients with HBV infection and alcoholism compared to patients with HBV infection or alcoholism alone. Future research efforts should focus on addressing the above issues.

## CONCLUSION

Taken together, the existing studies indicate that alcohol adversely affects HBV and HCV infections in the liver by promoting viral replication and oxidative stress and suppressing viral immune responses. Considering the findings that the interaction of alcohol with viral hepatitis (*e.g.*, HBV, HCV) contributes to the increased risk of developing HBV- or HCV-induced liver fibrosis, end-stage cirrhosis, and even deadly liver cancer, such as HCC, it is highly recommended that individuals with HBV or HCV infection abstain from alcohol to slow disease progression. In addition, these findings may have broader implications that abstaining from alcohol is needed for all individuals to protect the liver (Figure 1).

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Figure 1 was created with BioRender.com.

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