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Review

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# Factors predicting hepatocellular carcinoma in hepatitis C infection

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## Abstract

Hepatitis C virus (HCV) has emerged as a leading cause of hepatocellular carcinoma (HCC). In most cases, the virus causes HCC in the presence of chronic hepatic inflammation, advanced fibrosis, and cirrhosis. A combination of viral, environmental, and genetic factors are likely to determine the host immune response to the infection as well as the progression to HCC. Clinical and epidemiologic studies have identified many of the risk factors associated with HCC development in patients with chronic hepatitis C. Male sex and older age are considered as independent risk factors for HCC, while alcohol consumption accelerates fibrosis, increasing the risk for progression to HCC. Obesity, diabetes mellitus, nonalcoholic fatty liver disease, aflatoxin exposure and occult hepatitis B infection, all contribute to a higher HCC risk. HCV patients infected with HCV genotype 3 are also more likely to develop HCC and genetic variations such as single nucleotide polymorphisms, which may also alter the risk. Sustained virological response to the antiviral therapy results in significantly more favorable long-term outcomes. The incidence of HCC after HCV eradication is similar between patients treated with peginterferon plus ribavirin and direct-acting antiviral therapy.

**Keywords**: Hepatitis C, hepatocellular carcinoma, risk factors, alcohol, cirrhosis, diabetes, nonalcoholic fatty liver disease, directly acting antiviral agents

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer in men and ranks seventh among women. It is also the third leading cause of cancer-related deaths in the world[1,2]. Hepatitis C virus (HCV) has emerged as the foremost cause of HCC in many countries and has surpassed hepatitis B virus (HBV)

as a significant risk factor for the disease[3]. In the majority of cases, HCC in hepatitis C occurs following persistent liver insult in the form of chronic hepatic inflammation, advanced fibrosis and cirrhosis[4,5]. Recently, studies have also shown a direct role for HCV in cancer promotion with various HCV proteins demonstrating oncogenic properties[6]. Overall, a combination of viral, genetic, host and environmental factors likely influence HCC carcinogenesis[7]. Factors that thus affect or modify the likelihood of HCC development in patients with chronic hepatitis C, have been identified by clinical and epidemiologic studies. This review seeks to identify and analyze these diverse factors.

## AGE AND GENDER

Male sex and older age are independent risk factors for HCC in chronic hepatitis C patients[1,8-12]. In one study investigating a Chinese cohort, age > 55, and male sex were associated with an increased risk of developing HCC[13]. Multivariate analyses of another study showed that older age, truncal obesity, and diabetes were significant predictors of advanced disease and HCC[14,15]. Furthermore, a study on patients with transfusion-acquired HCV infection concluded that age at transfusion > 36 affected the risk for hepatic decompensation and was an independent risk factor for HCC development, alongside gender[16].

Interestingly, multiple pregnancies may also increase the risk of HCV-related HCC. This raises questions about the role of estrogens and other pregnancy-related hormones in the modulation of HCV infection and its progression to HCC in female patients[17].

## ALCOHOL ABUSE

Patients with a history of alcohol abuse have a significantly higher prevalence of HCV infection than the general population[18]. Furthermore, alcohol consumption in patients with chronic hepatitis C accelerates the process of fibrosis with an increased risk for progression to cirrhosis and HCC. Indeed, a study of 2235 patients with chronic hepatitis C, daily alcohol consumption of 50 g or greater was associated with a 34% increase in the rate of fibrosis progression[19]. A meta-analysis of 20 articles (published between 1995 and 2004), involving more than 15,000 HCV chronically infected persons, illustrated that the pooled relative risk of cirrhosis associated with heavy alcohol intake (defined in the range of at least 210-560 gram per week) was 2.33 [95% confidence interval (CI), 1.67-3.26][20].

Alcohol abuse has been shown to be a key independent predictor of progression to HCC[21,22]. The exact amount of alcohol that increases the risk of HCC in patients with HCV is unknown but it appears that even modest alcohol use can accelerate fibrosis and so the risk for HCC[23]. Indeed, a case-control study to evaluate the risk of HCC for HCV infection found that the odds ratio (OR) of HCC development in HCV RNA positive patients was 26.1 (95% CI: 12.6-54.0) among subjects with alcohol intake of 0-40 g/day and increased to 62.6 (23.3-168) and 126 (42.8-373) with an alcohol intake of 41-80 and greater than 80 g/day, respectively[24].

The progression to HCC may be the direct result of an increase in HCV replication and an attenuation of the antiviral action of interferon due to alcohol[25]. Impaired host cellular immunity (due to dendritic cell dysfunction)[26] and increased oxidative stress and mitochondrial injury[27] due to alcohol consumption, all contribute to the development of HCC.

## DIABETES AND NON-ALCOHOLIC FATTY LIVER DISEASE

Hepatitis C patients with obesity, diabetes mellitus, and/or non-alcoholic fatty liver disease (NAFLD) have a higher risk of developing HCC[28,29]. In fact, five of seven studies analyzing diabetes demonstrated significantly increased HCC risk associated with concurrent diabetes with effect sizes ranging from HR 1.73 (95% CI: 1.30-2.30) to RR 3.52 (95% CI: 1.29-9.24). Additionally, insulin resistance, as measured by HOMA-IR, was

also found to be significantly associated with HCV-related HCC[30]. Diabetes not only increases the risk of HCC in treatment-naïve chronic hepatitis C patients[31] but also in patients with eradicated HCV[1,9,12,32].

Meanwhile, one of three studies analyzing body mass index demonstrated a significant association with HCC risk (BMI ≥ 30.0 *vs.* BMI < 23; RR 4.13, 95% CI: 1.38-12.40) and two of the three studies analyzing steatosis demonstrated the significantly higher risk of HCC associated with steatosis[28]. Indeed, HCV patients in the US were found to progress more rapidly to HCC than their counterparts in China and the underlying fatty liver disease was found to be a major contributor to this difference[15].

## HEPATITIS B CORE ANTIBODY POSITIVITY

The risk of HCC increases in patients with hepatitis C who have occult hepatitis B infection or are hepatitis B core antibody positive[14,33]. In one study, the presence of hepatitis B core antigen was one of the independent predictors associated with the occurrence of HCC in HCV patients without advanced fibrosis[34]. On the other hand, HCV sero-status (positive *vs.* negative among patients with chronic hepatitis B may also increase the risk of HCC, independent of HBV viral load, with a HR of 2.5 (95% CI: 1.7-3.6)[35].

## AFLATOXIN

Significant contamination of food by aflatoxin is an additional risk factor for HCC in some parts of Asia[36,37]. While studies have shown synergism between aflatoxin and HBV in causing HCC, much less is known about whether aflatoxin and HCV synergize in a similar fashion. It is interesting to note that HCV prevalence itself is much higher in areas where aflatoxin exposure is also high[38].

## ADVANCED FIBROSIS AND CIRRHOSIS

HCC develops in hepatitis C patients mostly in the setting of advanced fibrosis and liver cirrhosis[13]. For patients without pre-existing cirrhosis, a higher Fibrosis-4 (FIB-4) index translates to a higher risk of HCC[39]. Untreated patients with cirrhosis have a significantly higher HCC incidence rate (45.3 per 1000 person-years) compared to those treated with either IFN or DAAs[40,41]. Moreover, liver cirrhosis, high AST to platelet ratio index (APRI) levels, and IL28B rs12979860 at baseline are all associated with HCC development in patients without sustained virological response (SVR) after peg-IFN combination therapy[42]. Even with SVR, the absolute risk of HCC is high in patients with established cirrhosis[1,8,9,12,43-46].

## HCV GENOTYPE

HCV patients infected with HCV genotype 3 are at higher risk for end-stage liver disease, HCC, and liver-related death compared to other genotypes[11,43]. This association is independent of patients' age, diabetes, body mass index, or antiviral treatment[43]. The risk of HCC remains high even after eradication of genotype 3 HCV[1,46-48]. This genotype may have a particular oncogenic mechanism, leading to HCC development even in non-cirrhotic patients[49]. Certain polymorphisms of the core, NS3, and NS5A proteins of HCV genotype 1b may be associated with the development of HCC[50].

## SINGLE NUCLEOTIDE POLYMORPHISMS

Genetic variations, such as single nucleotide polymorphisms (SNPs), may alter disease risk and thus may be used as predictive markers of disease outcome. A genome-wide association study found a strong association between the SNP rs17047200, located within the intron of the tolloid-like 1 gene (TLL1) on chromosome 4, and the development of HCC in patients who achieved an SVR after treatment for chronic HCV infection[9]. Additionally, the association of variants in patatin-like phospholipase domain containing 3 (PNPLA3) and the unfolded protein response regulator GRP78, with the risk of developing HCC, has been described in Italian

HCV patients[51]. Moreover, the reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) gene, a novel transformation suppressor gene, has also been linked to HCC amongst several other malignancies. However, a study conducted on an Egyptian cohort concluded that the RECK gene rs10814325 TT genotype could not be considered a risk factor for HCC development in hepatitis C patients, but may be related to the disease progression and metastasis[52].

Furthermore, the GG and GG + GA genotypes of IL17A gene may also serve as a risk factor for HCC development by increasing IL17 and IgE levels[53]. WT IL-23R GG[54], transforming growth factor-β1 (TGF-β1)-509 and tumor necrosis factor-α (TNF-α)-308 genes polymorphisms may also serve as risk factors for cirrhosis and HCC in chronic hepatitis C patients[55].

## NON-RESPONSE TO THE THERAPY

Antiviral therapy reduces the development of HCC and complications of cirrhosis in patients with chronic hepatitis C[56]. A risk scoring system has been developed to predict HCC development for HCV patients following antiviral therapies. The system includes age, gender, platelets count, alpha-fetoprotein levels, fibrotic stage, HCV genotype and response to the antiviral therapy[10].

The cumulative risk of HCC development is higher in subjects with high HCV RNA titer than subjects with low titer[45]. SVR results in significantly more favorable long-term outcomes, and decreased risk of progression to cirrhosis and HCC[13,57]. Indeed, a meta-analysis showed that SVR after treatment at any stage of fibrosis is associated with reduced HCC risk[58]. The risk of developing HCC diminishes significantly 2 years after SVR[44].

The risk of HCC after HCV eradication, though considerably reduced, remains relatively high at 0.33% per year[47]. Compared to subjects with spontaneous viral clearance, subjects with antiviral treatment-induced HCV viral clearance are at higher risk for HCC development, especially if they have significant hepatic fibrosis[12].

Antiviral therapy for patients with normal ALT levels can also lower the HCC incidence in responders, particularly for elderly and male patients[59]. Moreover, even in patients who have developed HCC within the Milan criteria and have undergone curative treatment for HCC, elimination of HCV and SVR inhibits recurrence and contributes to a preferential prognosis[60].

## DIRECTLY ACTING ANTIVIRAL AGENTS

The role of DAAs (used in the treatment of HCV) in the development of HCC is controversial, with several early studies demonstrating a tenuous link. However, a retrospective population-based cohort study of 17,836 patients treated with either an interferon-based regimen or DAA, showed that the risk of HCC was the same in both groups[40]. A meta-analysis of 41 studies further clarified the issue and concluded that the risks of HCC development after HCV eradication were similar between patients treated with peginterferon plus ribavirin and direct-acting antiviral therapy and that there was no evidence to suggest that DAAs promoted HCC[8,61]. The seemingly higher incidence of HCC following SVR with DAA therapy was related to baseline risk factors and patient selection, and not the use of interferon-free therapy *per se*. The cohort of patients treated with DAAs in earlier studies included older patients and patients with more advanced cirrhosis who were already predisposed to a higher risk for HCC at baseline. In a cohort study of 857 patients, individuals receiving interferon-free therapy were more likely to be older, of white ethnicity, Child-Turcotte-Pugh B/C *vs.* Child-Turcotte-Pugh A; thrombocytopenic, non-genotype 3, and treatment experienced. HCC occurrence was observed in 46 individuals during follow-up. In univariate analysis, IFN-free therapy was associated with a significantly increased risk of HCC (HR: 2.48; $P = 0.021$). However, after multivariate adjustment for baseline factors, no significant risk attributable to interferon-free therapy persisted[41].

Among patients treated with DAA, SVR is associated with a considerable reduction in the risk of HCC. However, in patients with SVR, the absolute risk of HCC remains high in patients with established cirrhosis[62].

## CONCLUSION

Hepatitis C accounts for the majority of the cases of HCC in many parts of the world. HCC typically occurs in patients with advanced hepatic fibrosis or cirrhosis in the setting of chronic inflammatory state induced by HCV. Clinical and epidemiologic studies have identified host and viral factors associated with HCC development in patients with HCV infection. Direct-acting antiviral drugs do not increase the risk of developing HCC. Sustained virological response to the antiviral therapy results in significantly more favorable long-term outcomes.

## DECLARATIONS

### Authors' contributions

Both authors contributed by literature review and manuscript writing, editing and review.

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

Both authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.



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