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ORIGINAL RESEARCH

Eradication of Hepatitis C Virus (HCV) Improves Survival of Hepatocellular Carcinoma Patients with Active HCV Infection – A Real-World Cohort Study

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Background: Hepatocellular carcinoma (HCC) caused by hepatitis C virus (HCV) infection has become less and less due to the use of direct-acting antiviral agents (DAAs). Although it may be common to assume that eradication of the virus should improve the survival of HCC patients, large-scale randomized clinical data to support the correlation between viral load and prognosis are still lacking in China. The aim of the study was to evaluate the efficacy of antiviral therapy for HCC patients with active HCV infection.

Patients and Methods: We retrospectively enrolled 80 HCC patients with active HCV infection. Active HCV infection was defined as positive for HCV antibody with detectable HCV RNA by polymerase chain reaction.

Results: Forty-four patients (55.0%) received interferon combined with ribavirin treatment and 23 patients achieved sustained virological response (SVR). The 1-year survival rate in patients who achieved SVR was the highest, followed by those with non-SVR after antiviral treatment, and those without antiviral therapy (1-year survival rate were 91.3%, 88.4%, and 73.1%, respectively, P = 0.012). In the univariate analysis, alcohol intake and alpha-fetoprotein >20 ng/mL were associated with lower overall survival (OS) (P = 0.025 and P = 0.044, respectively), while SVR after antiviral treatment was associated with longer OS (P = 0.016). In the multivariate analysis, only SVR after antiviral treatment was significantly associated with OS (P = 0.014).

Conclusion: Our results ensured that the elimination of HCV substantially improved OS in HCC patients with active HCV infection, and the prognosis of those patients without antiviral therapy was poor.

Keywords: hepatocellular carcinoma, active hepatitis C virus infection, sustained virological response, survival

Introduction

The major underlying etiologies of hepatocellular carcinoma (HCC) include chronic viral hepatitis, alcohol intake, cirrhosis, and aflatoxin exposure.[1–3] Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the leading causes of HCC and are responsible for more than 80% of HCC cases worldwide.[2] In China, the latest data indicated that the morbidity and mortality rates associated with HCC were ranked fourth and third, respectively. HCV-related HCC, which accounts for 27.7% of HCC cases, represents a significant health burden.[4] HCV replication was

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correlated with ongoing liver damage. Despite the severity of chronic HCV infection, there are fewer patients treated for HCV in China.[5]

HCV is an RNA virus that replicates exclusively in the cytoplasm of hepatocytes and does not integrate its genetic material into the host genome. Therefore, HCV requires continuous replication to maintain an active infection. HCV-related HCC results from chronic inflammation, immune-mediated hepatocyte death, and progression to cirrhosis.[6,7] Interferon (IFN)-based regimens have been reported to reduce HCV, but not eliminate, and future risk of development of HCC through prevention of progression to cirrhosis.[8] Direct-acting antiviral agents (DAAs) can further increase the sustained virological response (SVR) rate even to over 90% and have become the new standard for the treatment of HCV.[9,10] However, the high financial cost of DAAs limits the usage, and IFN combined with ribavirin is still the standard treatment in China.[11] In a meta-analysis of observational studies of HCV-related HCC patients, SVR following IFN-based therapy was associated with improved OS.[12] However, compared to cancer treatment, antiviral therapy was often ignored by Chinese patients due to limited understanding.

HCC caused by HCV infection has become less and less in recent years due to the use of DAAs. Although it may be common to assume that eradication of the virus should improve the survival of HCC patients, large-scale randomized clinical data to support the correlation between viral load and prognosis are still lacking in China. The study aimed to evaluate the efficacy of antiviral therapy for HCC patients with active HCV infection.

The present retrospective study aimed to evaluate the impact of antiviral therapy and HCV eradication on clinical outcomes of HCC patients with active HCV infection in a monocentric cohort representing a real-world Chinese setting.

Patients and Methods

Study Population

This retrospective cohort included 80 HCC patients with active HCV infection seen at the Cancer Hospital, Chinese Academy of Medical Sciences, between May 2014 and January 2019. Active HCV infection was defined as positive for HCV antibody with detectable HCV RNA. Serum HCV RNA was determined by RT-PCR of plasma using Roche's LightCycler 480 Ⅱ fluorescence quantitative PCR/HCV nucleic acid quantitative detection reagent (Kehua Bio-engineering, Shanghai, CN), which quantifies HCV RNA with a limit of detection of 15 IU/mL. The exclusion criteria were as follows: (1) a follow-up period of less than 6 months without death; (2) seropositivity for HBV surface antigen; and (3) seropositivity for human immunodeficiency virus antibody. Diagnosis of HCC was confirmed using histological findings or typical imaging characteristics according to the guidelines of the European Association for the Study of the Liver (EASL).[2] All patients provided written informed consent. This study was approved by Cancer Hospital, Chinese Academy of Medical Sciences ethics committee, and that it was conducted in accordance with the Declaration of Helsinki. Clinical information for each patient was obtained from medical records.

Data Collection and Patient Follow-Up

Demographic data and information regarding alcohol consumption, smoking habits, and antiviral treatment history were extracted from the medical records of the patients included in the study. All patients underwent HCV RNA tests and serological testing to determine the presence of HBsAg, anti-HIV, and anti-HCV, alpha-fetoprotein (AFP) levels, liver biochemical parameters, and blood cell counts prior to starting treatment.

The diagnostic criteria for liver cirrhosis included the presence of portal hypertension manifested as splenomegaly, thrombocytopenia <100,000/mm^3, ascites, varices, or hepatic encephalopathy, and imaging findings consistent with liver cirrhosis.[13]

Initial treatment strategies for HCC during the study period were surgical resection, radiofrequency ablation (RFA), chemoembolization (TACE), radiotherapy, and sorafenib. Curative treatment strategies included hepatic resection and RFA. IFN combined with ribavirin was administered for at least 24 weeks as antiviral therapy. SVR was defined as undetectable HCV RNA in the blood at 12 weeks after completion of antiviral treatment.

Follow-up was completed in January 2020. Overall survival (OS) was defined as the period from the date of HCC diagnosis to the confirmed death date of patients who died, or the date of the last follow-up for surviving patients.

Statistical Analysis

Comparisons between variables were performed using One-Way ANOVA or Kruskal–Wallis *H*-test for numerical variables, and the Chi-Squared test for categorical variables. Survival curves were constructed using the Kaplan–Meier method and compared using the Log-rank test. The

Cox proportional hazards model was used for univariate and multivariate analysis. Candidate prognostic factors with a significance level ≤0.10 in the univariate analysis were included in the multivariate analysis. The risk was expressed as a hazard ratio and a 95% CI. All statistical tests were two-sided and considered significant when $p < 0.05$. Statistical analyses were performed using SPSS 22.0 and GraphPad Prism 7 was used to plot figures.

Results

Patients Characteristics

Eighty HCC patients with active HCV infections were included in this study, including 61 (76.3%) males and 19 females (ratio 3.2:1). Patient ages ranged from 48 to 82, with an average age of 63.3 years (95% CI: 61.5–65.0). Approximately half of the patients (41.3%) had a history of alcohol use, 47 patients (58.8%) had cirrhosis, and the majority (98.8%) of cases were classified as Child-Pugh A. Forty-four patients (55.0%) received antiviral treatment, and only 23 patients (23/44, 52.3%) achieved SVR. Hematological parameters, liver function markers, coagulation function markers, and tumor characteristics were compared between the patients received antiviral therapy with SVR, those treated without SVR and those not treated, and no significant differences were observed (Table 1). The tumor characteristics and treatment modalities of the entire cohort are summarized according to TNM stage in Table 2.

Overall Survival Rate

Follow-up data were available for all patients, and the median follow-up time was 2.03 years (range: 0.40–5.38 years). During the follow-up period, 29 patients (36.3%) died of recurrence or distant metastasis, and four patients died of liver failure. The 1- and 3-year overall survival rates were 83.0% and 57.4%, respectively.

The 1- and 3-year OS rates in patients who received antiviral therapy with SVR were 91.3% and 80.1%, respectively, followed by those treated without SVR (88.4% and 54.6%, respectively), higher than those without antiviral treatment (73.1% and 39.5%, respectively) (P=0.012). The 1- and 3-year OS rates for the group that used alcohol (76.6% and 41.9%, respectively) were significantly lower than those who did not use alcohol (87.8% and 68.5%, respectively, P=0.025). Similarly, patients with AFP > 20 ng/mL had inferior OS (P = 0.044) compared to those with AFP ≤ 20 ng/mL. Kaplan–Meier plots for OS as a function of the effect of antiviral therapy, alcohol intake, and AFP value are shown in Figures 1–3.

Table 1 Baseline Characteristics of the Entire Cohort According to Virological Response and Antiviral Treatment (n = 80)

Features	Without Antiviral Treatment	Antiviral Treatment with Non-SVR	Antiviral Treatment with SVR	*P* value
Cases	36	21	23	
Demographic				
Age (years)	63.6±7.9	63.5±8.0	62.6±7.7	0.890[†]
Sex, male	30(83.3%)	14(66.7%)	17(73.9%)	0.344[§]
Hematological parameters				
Hemoglobin (g/L)	145.5(19)	136.0(24)	141.0(24)	0.509[‡]
Platelet (× 10^9/L)	151.6±76.5	126.4±55.1	143.2±51.7	0.373[†]
Liver function markers				
Total bilirubin (μmol/L)	15.2(6.6)	15.0(10.7)	12.7(6.5)	0.665[‡]
Albumin (g/L)	40.7±5.1	41.3±4.2	41.8±3.9	0.625[†]
ALT (U/L)	41.5(70)	67.0(66)	62.0(64)	0.699[‡]
Coagulation function markers				
Prothrombin time(s)	12.1(1.6)	12.2(1.1)	11.7(2.0)	0.292[‡]
Characteristics of tumor				
AFP> 20 ng/mL	19(52.8%)	12(57.1%)	12(52.2%)	0.935[§]
Multiple lesions	11(30.6%)	6(28.6%)	5(21.7%)	0.754[§]

Notes: [†]One-way ANOVA was used for analysis and data were presented as mean ± standard deviation. [‡]Kruskal–Wallis *H*-test was used for analysis and data were presented as median (interquartile range). [§]Chi-squared test was used for the comparison and data were presented as number (percentage).
Abbreviations: SVR, sustained virological response; ALT, alanine transaminase; AFP, alpha-fetoprotein.

Table 2 Tumor Characteristics and Treatment Modalities of the Entire Cohort According to TNM (n = 80)

Features	I(n=28)	II(n=32)	III(n=17)	IV(n=3)
Characteristics of tumor				
AFP> 20 ng/mL	9(32.1%)	19(59.4%)	12(70.6%)	3(100.0%)
Tumor size (cm)	2.80±2.4	4.05±2.5	6.97±2.63	5.53±5.71
Multiple lesions	0	13(40.6%)	8(47.1%)	1(33.3%)
Treatment modality				
Resection	12(42.9%)	9(28.1%)	6(35.3%)	0
RFA	9(32.1%)	8(25.0%)	1(5.9%)	2(66.7%)
TACE	8(28.6%)	23(71.9%)	12(70.6%)	2(66.7%)
Radiotherapy	3(10.7%)	2(6.3%)	1(5.9%)	0
Sorafenib	0	0	1(5.9%)	1(33.3%)
Curative treatment (initial)	21(75.0%)	15(46.9%)	7(41.2%)	2(66.7%)
Recurrence after curative treatment (n=45)	11(52.4%)	10(66.7%)	5(71.4%)	0
one-year survival rate	92.1%	82.9%	72.4%	50.0%

Note: Chi-squared test was used for the comparison between the different TNM stages.
Abbreviations: AFP, alpha-fetoprotein; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; OS, overall survival.

Univariate and Multivariate Analyses

Univariate survival analysis of OS was performed using 10 variables: gender, age, smoking history, alcohol intake, AFP level, HCV-RNA level, antiviral treatment, liver cirrhosis, tumor size, and tumor number. According to the univariate analysis, alcohol intake (P = 0.028) and AFP > 20 ng/mL (P = 0.048) were predictors of shorter survival, and SVR after antiviral therapy was a predictor of longer survival. Multivariate analysis confirmed that only SVR after antiviral therapy was an independent predictor of OS for HCC patients with active HCV infection [hazard ratio = 0.555; 95% confidence interval, 0.347–0.886; P=0.014] (Table 3).

Discussion

Progression of chronic hepatitis C (CHC)-related liver damage is associated with continuous viral replication and may lead to fibrosis and cirrhosis, eventually HCC development. The goal of anti-HCV therapy is to reduce liver inflammation. Anti-HCV therapy may improve liver function in patients with CHC.[6] In addition, the cure of HCV may prolong the OS of HCC patients due to liver function reserves.[14] This retrospective study included HCC patients with active HCV infections in China and showed that HCV eradication could improve survival in these patients. In our cohort, patients who achieved SVR after IFN combined with ribavirin had longer OS than those who did not get SVR or those without antiviral treatment. Multivariate analysis showed that SVR was an

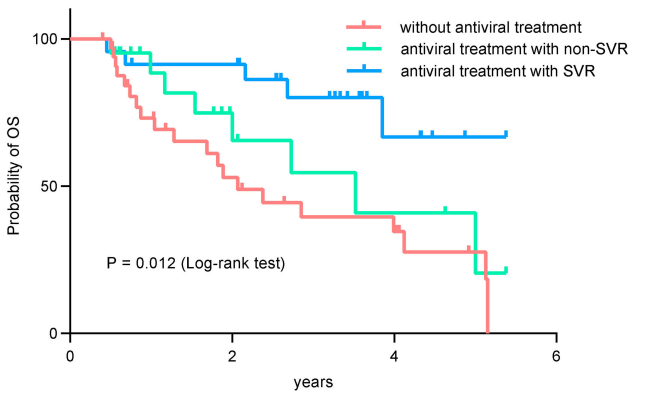

Figure 1 Kaplan–Meier survival curve for OS based on virological response and antiviral treatment in patients HCC with active HCV infection.

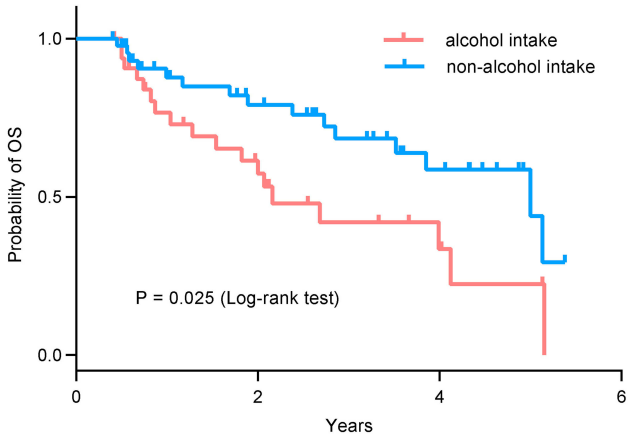

Figure 2 Kaplan–Meier survival curve based on alcohol intake in HCC patients with active HCV infection.

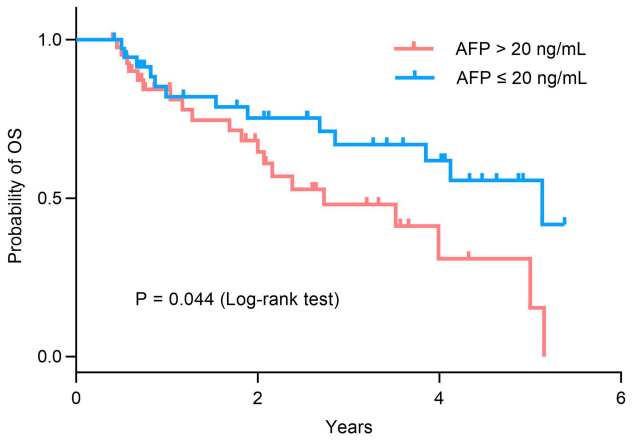

Figure 3 Kaplan–Meier survival curve based on AFP levels in HCC patients with active HCV infection.

independent predictor of longer survival (HR = 0.555; P = 0.014). However, in our study, only 44 patients received antiviral treatment, and the SVR rate was 52.3%. The virological response rate was similar to that observed in a previous study of patients with HCC and CHC,[9] but the rate of antiviral treatment was quite low. This low rate of antiviral treatment may have been due to limited knowledge, asymptomatic HCV, the high price of medication, and scary of adverse events, such as high fever, general fatigue, loss of appetite, and platelet count reduction. Pegylated interferon (Peg-IFN)-based therapy was reported to achieve a higher SVR in the treatment of CHC than conventional IFN therapy.[15,16] Several studies have found that Peg-IFN-based therapy could improve the survival rates after curative treatment of hepatitis-related HCC with no severe adverse effects.[17,18] Our study showed that HCV eradication improved survival in HCC patients with active HCV infections. The results of our study could guide antiviral treatment plans for HCC patients with active HCV infections.

In past years, DAAs have revolutionized the treatment of CHC, with a significant improvement of efficacy, shortened treatment duration, and tolerability.[9,10] However, two articles suggested an unexpectedly higher rate of early occurrence and recurrence of HCC in HCV-infected patients who were treated with DAAs in 2016.[19,20] It was postulated that a rapid decrease of HCV viral load in the short term after DAAs may contribute to early tumor development. Sasaki et al[21] demonstrated the changes of complement cascades and neutralizing antibodies after SVR by DAAs therapy, and both complement cascades and neutralizing antibodies were important for HCC cells survival. However, several articles presenting the opposite data from longer-term follow-up periods have been published.[22,23] Thus, a conclusion has not been reached in this matter and future studies should focus on whether there is a risk or advantage of HCC recurrence or occurrence with IFN-free therapy.

In this study, all included patients received some form of treatment. This showed that our patients were treated more aggressively. The 1- and 3-year overall survival rates for the entire cohort were 83.0% and 57.4%, respectively, which were similar to those observed in a previous study.[24] In another previous study,[25] the 1- and 3-year survival rates of patients with HCV-related HCC were 68% and 40%, which were lower than the results observed in our study (83.0% and 57.4%, respectively).

Table 3 Univariate and Multivariate Analyses Showing Significant Predictive Factors of Mortality in HCC Patients with Active HCV Infection (N= 80)

Variables		OS					
		Univariate Analysis			Multivariable Analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Sex	female vs male	0.430	0.151–1.228	0.115			
Age (years)	> 65 vs ≤ 65	0.964	0.480–1.935	0.917			
Smoking history	yes vs no	1.600	0.801–3.193	0.183			
Alcohol intake	yes vs no	2.166	1.085–4.323	0.028	1.768	0.880–3.551	0.109
AFP (ng/mL)	> 20 vs ≤ 20	2.053	1.005–4.195	0.048	1.785	0.873–3.650	0.112
HCV-RNA (IU/mL)	high vs low	0.997	0.484–2.052	0.993			
Virological response	treated with SVR vs treated without SVR vs not treated	0.521	0.334–0.815	0.004	0.555	0.347–0.886	0.014
Liver cirrhosis	yes vs no	1.286	0.629–2.630	0.491			
Tumor size (cm)	> 5 vs ≤5	1.242	0.603–2.557	0.557			
Tumor number	multiple vs single	1.471	0.695–3.115	0.313			

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; AFP, alpha-fetoprotein.

In the present study, the factors associated with inferior OS were high AFP level and alcohol intake. Currently, AFP is the only tumor marker had been used for screening and diagnosing of HCC.[26] However, in our study, only 27.5% of patients had AFP levels greater than 400 ng/mL, and the median AFP value was 28.6 ng/mL, which was similar to the results of other studies.[23,24] Soresi et al[27] showed that the positive predictive value of AFP for patients with viral HCC was significantly lower than that for patients with non-viral HCC. Yoshimasu et al[28] reported that AFP value was independently related to the occurrence and recurrence of HCC in patients with CHC. In our study, AFP > 20 ng/mL was strongly associated with later tumor stage and shorter OS.

During HCC progression, several environmental factors such as aflatoxin B1, alcohol consumption, and hepatotoxic chemical agents may synergize and result in progressive accumulation of multiple genomic changes in hepatocytes.[29] Alcohol consumption induces liver damage through endotoxins, oxidative stress, and inflammation,[30] and alcohol induces synergistic effects with HCV that increase the risk for the development of HCC.[31] Alcohol is the most important factor in chronic hepatitis progression. A recent study showed that the combined effects of alcohol and HCV augmented free radical formation in the liver, and reduced the antioxidant capacity of the liver.[32] In our population, alcohol intake was associated with an inferior OS ($P = 0.025$), which confirmed that alcohol consumption could influence disease outcome.

A previous study showed that HCV-Ab levels predicted HCC recurrence, especially for late recurrence due to presumed multicentric carcinogenesis.[33] Furthermore, low HCV viral load predicted better long-term surgical outcomes in patients with HCC independent of serologic eradication of HCV.[34] Univariate analysis showed that HCV RNA levels (>600,000 IU/mL) were not associated with survival in patients with HCC (P = 0.993, 95% CI = 0.484–2.052) in our study. However, our results were similar to those in previous studies.[35,36] It has been reported that advanced liver fibrosis is an important risk factor for HCC.[37] However, in our study, cirrhosis was not associated with OS after the IFN combined with ribavirin therapy. On the contrary, it suggested that the outcome was significantly associated with SVR. Since a majority of cases in the study were mild or moderate cirrhosis with nearly all of the cases were classified as Child-Pugh A, it suggested the possibility that the degree and rate of cirrhosis are the risk factors affecting the prognosis of HCV-related HCC. Moreover, there was no correlation between the outcome and the maximum tumor size and multiple occurrences. It suggested that the prognosis was closely related to the malignancy of HCC, such as a high AFP level.

As with all real-world studies, our study also suffered from several limitations. For example, HCV genotyping was not performed in our hospital, and Park[24] reported that patients with genotype 2 had a longer median OS than patients with genotype 1 or genotype 3. The detective level of the majority of hospitals in China was similar to us, so our results could still provide useful information for the treatment of HCC patients with HCV infection. This study was a retrospective study, and patients with poor economy and low education level were more likely to reject antiviral treatment, and the prognosis of these patients was also poor because they were easy to receive unregular anticancer treatment. Additionally, the sample size in our study was relatively small. In future, we will follow up more cases to find more valuable data.

In conclusion, anti-HCV therapy should be routinely used as part of the treatment of HCC patients with active HCV infection and those patients with SVR get the most benefits.

Data Sharing Statement

Data and material will be available upon corresponding author approval. All data sets analyzed for this study are included in the manuscript and the additional files.

Ethics Approval and Consent to Participate

Informed consent was obtained from all patients and the protocol was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med*. 2011;365(12):1118–1127. doi:10.1056/NEJMra1001683
2. Galle PR, Forner A, Llovet JM, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182–236. doi:10.1016/j.jhep.2018.03.019
3. Fitzmaurice C, Akinyemiju T, Abera S, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level results from the global burden of disease study 2015. *JAMA Oncol*. 2017;3(12):1683–1691. doi:10.1001/jamaoncol.2017.3055
4. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115–132. doi:10.3322/caac.21338
5. Zhang JY, Bin LZ, Zhang L, et al. DOES IT WORK? -a randomized controlled trial to test the efficacy of HCV and HIV-related education on drug users in MMT, China. *BMC Infect Dis*. 2019;19(1):774. doi:10.1186/s12879-019-4421-5
6. Bandiera S, Billie Bian C, Hoshida Y, Baumert TF, Zeisel MB. Chronic hepatitis C virus infection and pathogenesis of hepatocellular carcinoma. *Curr Opin Virol*. 2016;20:99–105. doi:10.1016/j.coviro.2016.09.010
7. Vescovo T, Refolo G, Vitagliano G, Fimia GM, Piacentini M. Molecular mechanisms of hepatitis C virus–induced hepatocellular carcinoma. *Clin Microbiol Infect*. 2016;22(10):853–861. doi:10.1016/j.cmi.2016.07.019
8. Li DK, Chung RT. Impact of hepatitis C virus eradication on hepatocellular carcinogenesis. *Cancer*. 2015;121(17):2874–2882. doi:10.1002/cncr.29528
9. Feld JJ, Jacobson IM, Hode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med*. 2015;373(27):2599–2607. doi:10.1056/NEJMoa1512610
10. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV Genotype 2 and 3 infection. *N Engl J Med*. 2015;373(27):2608–2617. doi:10.1056/NEJMoa1512612
11. Chinese Society of Hepatology and Chinese Society of Infectious Diseases, Chinese Medical Association. The guideline of prevention and treatment for chronic hepatitis C: a 2015 update. *Chin J Liver Dis*. 2015;7:19–35.
12. Hsu C-S, Chao Y-C, Lin HH, Chen D-S, Kao J-H. Systematic Review: impact of Interferon-based Therapy on HCV-related Hepatocellular Carcinoma. *Sci Rep*. 2015;5(1):9954. doi:10.1038/srep09954
13. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2016. *J Hepatol*. 2017;66(1):153–194. doi:10.1016/j.jhep.2016.09.001
14. Huang CF, Yu ML. Direct-acting antivirals response in hepatocellular carcinoma: does the presence of hepatocellular carcinoma matter? Clin. *Mol Hepatol*. 2019;25(2):168–171. doi:10.3350/cmh.2018.1014
15. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet*. 2001;**358**:958–965.
16. Teng W, Hsieh YC, Lui KW, et al. Eradication of hepatitis C virus profoundly prolongs survival in hepatocellular carcinoma patients receiving transarterial chemoembolization. *Viral Hepat*. 2017;24(12):1160–1167. doi:10.1111/jvh.12745
17. Ishikawa T, Higuchi K, Kubota T, et al. Combination PEG-IFN a-2b/ribavirin therapy following treatment of hepatitis C virus-associated hepatocellular carcinoma is capable of improving hepatic functional reserve and survival. *Hepatogastroenterology*. 2012;59(114):529–532. doi:10.5754/hge10867
18. Hagihara H, Nouso K, Kobayashi Y, et al. Effect of pegylated interferon therapy on intrahepatic recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. *Int J Clin Oncol*. 2011;**16**:210–220.
19. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. *J Hepatol*. 2016;65(4):727–733. doi:10.1016/j.jhep.2016.06.015
20. Reig M, Mariño Z, Perelló C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol*. 2016;65(4):719–726. doi:10.1016/j.jhep.2016.04.008
21. Sasaki R, Meyer K, Moriyama M, et al. Rapid hepatitis C virus clearance by antivirals correlates with immune status of infected patients. *J Med Virol*. 2019;91(3):411–418. doi:10.1002/jmv.25310
22. Nakano M, Koga H, Ide T, et al. Predictors of hepatocellular carcinoma recurrence associated with the use of direct-acting antiviral agent therapy for hepatitis C virus after curative treatment: a prospective multicenter cohort study. *Cancer Med*. 2019;8(5):2646–2653. doi:10.1002/cam4.2061
23. Singal AG, Rich NE, Mehta N, et al. Direct-acting antiviral therapy for hepatitis C virus infection is associated with increased survival in patients with a history of hepatocellular carcinoma. *Gastroenterology*. 2019;**157**:1253–1263.e2.
24. Park HK, Lee SS, Bin IC, al E. Hepatitis C virus genotype affects survival in patients with hepatocellular carcinoma. *BMC Cancer*. 2019;19(1):822. doi:10.1186/s12885-019-6040-3
25. Sinn DH, Gwak GY, Cho J, Paik SW, Yoo BC. Comparison of clinical manifestations and outcomes between hepatitis B virus- and hepatitis C virus-related hepatocellular carcinoma: analysis of a nationwide cohort. *PLoS One*. 2014;9(11):e112184. doi:10.1371/journal.pone.0112184
26. Liu X, Meng J, Xu H, Niu J. Alpha-fetoprotein to transaminase ratio is related to higher diagnostic efficacy for hepatocellular carcinoma. *Medicine (Baltimore)*. 2019;98(17):e15414. doi:10.1097/MD.0000000000015414
27. Soresi M, Magliarisi C, Campagna P, et al. Usefulness of alpha-fetoprotein in the diagnosis of hepatocellular carcinoma. *Anticancer Res*. 2003;23(2C):1747–1753.
28. Yoshimasu Y, Furuichi Y, Kasai Y, et al. Predictive factors for hepatocellular carcinoma occurrence or recurrence after direct-acting antiviral agents in patients with chronic hepatitis C. *J Gastrointest Liver Dis*. 2019;28(1):63–71. doi:10.15403/jgld.2014.1121.281.hpc
29. Tornesello ML, Buonaguro L, Izzo F, Buonaguro FM. Molecular alterations in hepatocellular carcinoma associated with hepatitis B and hepatitis C infections. *Oncotarget*. 2016;7(18):25087–25102. doi:10.18632/oncotarget.7837
30. Testino G, Leone S, Borro P. Alcohol and hepatocellular carcinoma: a review and a point of view. *World J Gastroenterol*. 2014;20(43):15943–15954. doi:10.3748/wjg.v20.i43.15943
31. Osna NA, Ganesan M, Donohue TM. Proteasome- and ethanol-dependent regulation of HCV-infection pathogenesis. *Biomolecules*. 2014;4(4):885–896. doi:10.3390/biom4040885
32. Safdar K, Schiff ER. Alcohol and hepatitis C. *Semin Liver Dis*. 2004;24(3):305–315. doi:10.1055/s-2004-832942
33. Uemura M, Sasaki Y, Yamada T, et al. Serum antibody titers against hepatitis C virus and postoperative intrahepatic recurrence of hepatocellular carcinoma. *Ann Surg Oncol*. 2014;21(5):1719–1725. doi:10.1245/s10434-013-3417-4
34. Shindoh J, Hasegawa K, Matsuyama Y, et al. Low hepatitis c viral load predicts better long-term outcomes in patients undergoing resection of hepatocellular carcinoma irrespective of serologic eradication of hepatitis c virus. *J Clin Oncol*. 2013;31(6):766–773. doi:10.1200/JCO.2012.44.3234
35. Akamatsu M, Yoshida H, Shiina S, et al. Neither hepatitis C virus genotype nor virus load affects survival of patients with hepatocellular carcinoma. *Eur J Gastroenterol Hepatol*. 2004;16(5):459–466. doi:10.1097/00042737-200405000-00004

36. McMahon BJ, Bruden D, Townshend-Bulson L, et al. Infection with hepatitis c virus genotype 3 is an independent risk factor for end-stage liver disease, hepatocellular carcinoma, and liver-related death. *Clin Gastroenterol Hepatol*. 2017;15(431–437.e2):431–437.e2. doi:10.1016/j.cgh.2016.10.012

37. Wu CK, Chang KC, Hung CH, et al. Dynamic α-fetoprotein, platelets and AST-to-platelet ratio index predict hepatocellular carcinoma in chronic hepatitis C patients with sustained virological response after antiviral therapy. *J Antimicrob Chemother*. 2016;71(7):1943–1947. doi:10.1093/jac/dkw097