Assessment of hepatocellular carcinoma risk based on peg-interferon plus ribavirin treatment experience in this new era of highly effective oral antiviral drugs

Seung Ho Lee, MD, Young-Joo Jin, MD, PhD∗, Jun Young Shin, MD, Jin-Woo Lee, MD, PhD

Abstract
In this new era of highly effective oral antiviral drugs for chronic hepatitis C virus (HCV), indications for antiviral treatment may be extendable. This study undertaken to identify suitable candidates for peg-interferon plus ribavirin (PEG-IFN/RBV) treatment by evaluating hepatocellular carcinoma (HCC) risk in patients with chronic HCV treated or not with PEG-IFN/RBV.

This large-scale retrospective study was conducted on 1176 patients with chronic HCV without a history of HCC (treatment group [n = 489] and no-treatment group [n = 687]). In the treatment group, patients treated with PEG-IFN/RBV were dichotomized based on the achievement of sustained virologic response (SVR) into SVR (+) and SVR (−) groups.

Median follow-up for all study subjects was 31 months (range 6–144 months). Three-year cumulative HCC development rates in the SVR (+) (1.1%) and SVR (−) (8.6%) subgroups were significantly lower than in the no-treatment group (13.5%) (P < 0.01 and P < 0.01, respectively). In all study subjects, presence of cirrhosis (hazard ratio [HR], 9.92, P < 0.01), age (HR 1.03, P < 0.01), SVR (−) (HR 7.02, P < 0.01), and no-treatment (HR 6.76, P < 0.01) were found to be independent risk factors of HCC development. In the treatment group, age, the presence of cirrhosis, and SVR (−) were predictors of HCC development. In the no-treatment group, age, male, and the presence of cirrhosis were independent predictors for HCC development.

HCC risk increased in patients with chronic HCV with older age, cirrhosis, SVR (−) after PEG-IFN/RBV treatment, and no PEG-IFN/RBV treatment. Active antiviral therapy based on highly effective oral drugs needs to be considered in these patients.

Abbreviations: AFP = alpha-fetoprotein, ALT = alanine aminotransferase, BMI = body mass index, CHC = chronic HCV, DAAs = direct-acting antiviral, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, IFN = interferon, LC = liver cirrhosis, PEG-IFN/RBV = peg-interferon plus ribavirin, SVR = sustained virologic response, USG = ultrasonography.

Keywords: age, chronic hepatitis C, hepatocellular carcinoma, liver cirrhosis, sustained virologic response

1. Introduction
Hepatitis C virus (HCV) has infected about 180 million population worldwide and is the major cause of liver cirrhosis (LC) and hepatocellular carcinoma (HCC).[1,2] Since these diseases are associated with high mortality in the presence of chronic HCV (CHC), antiviral therapy for HCV infection could theoretically improve prognosis by preventing the development of LC or HCC. However, a substantial proportion of patients with CHC do not receive antiviral therapy.[3] Moreover, previous peg-interferon plus ribavirin (PEG-IFN/RBV)-based regimens are less effective and have higher side effect rates than direct-acting antiviral (DAA) agents and are contraindicated in patients prone to severe adverse events.[1,3–9]

Although previous studies have reported that the achievement of sustained virologic response (SVR) on antiviral therapy reduces the risk of HCC development, the majority were limited due to use of a conventional IFN regimen.[10–13] After the introduction of the more effective PEG-IFN/RBV therapy, several studies reported that failure to achieve SVR on PEG-IFN/RBV therapy, an advanced age, and LC were associated with unfavorable long-term outcomes or HCC development.[16–21] However, unfortunately, these studies were limited to bridging fibrosis or patients with LC.[14,20,21] and did not include patients who did not receive antiviral therapy.[16–21]

The paradigm for antiviral therapy in patients with CHC has rapidly changed from PEG-IFN-based therapy to DAA agents. After the FDA approved of DAA in 2011, new drugs, such as sofosbuvir and daclatasvir/asunaprevir, were recently approved with much higher SVR rates and lower adverse event rates than PEG-IFN/RBV.[7–9] Given that SVR rate improvement may translate into improved long-term prognosis in patients with CHC, active antiviral therapy with these new drugs needs to be applied to as many patients as possible. To date, however, selection criteria for treatment with these new drugs have not been fully determined.

Editor: Akiyoshi Kinoshita.

SHL and Y-JJ were responsible for the concept and design of the study, the acquisition, analysis and interpretation of the data, and the drafting of the manuscript. JYS and J-WL helped with data acquisition of the manuscript. The authors have no conflicts of interest to disclose.

Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, South Korea.

*Correspondence: Young-Joo Jin, Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, 27 Inhang-ro, Jung-gu, Incheon 400-711, South Korea (e-mail: jjyj412@hanmail.net).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2017) 96(16):e5321

Received: 7 June 2016 / Received in final form: 12 October 2016 / Accepted: 12 October 2016

http://dx.doi.org/10.1097/MD.0000000000005321
In the present study, therefore, we assessed the risk factors of HCC development in patients with CHC who had been treated with PEG-IFN/RBV or not, and sought to identify candidates for active anti-HCV therapy based on these risk factors in the new era of highly effective oral anti-HCV drugs.

2. Patients and methods

2.1. Study population

A total of 2578 patients registered at our institution between January 2004 and December 2013 were initially positive for HCV antibody and had no other chronic liver disease, such as hepatitis B virus (HBV) infection, alcoholic liver disease, autoimmune hepatitis, primary biliary cirrhosis, or Wilson disease (Fig. 1). Anti-HCV and HCV RNA levels were positive for more than 6 months in all patients. Of these 2578 patients, those who did not undergo an examination of HCV RNA (n = 445), negative for HCV RNA (n = 514), follow-up < 6 months, and those with a history of HCC or another malignancy (n = 67) were excluded. Of the remaining 1292 patients, 81 treated with a conventional interferon (IFN)-based therapy and 35 with a new drugs (n = 35) were also excluded. Patients treated with PEG-IFN/RBV after conventional IFN-based therapy were enrolled in the study. Accordingly, 1176 patients were finally enrolled in this study, and their database records were retrospectively analyzed.

The 1176 study subjects were allocated to a no-treatment group (n = 687) or a treatment group (n = 489). Patients in the treatment group were treated with PEG-IFN (alfa-2a or alfa-2b)/RBV for 24 or 48 weeks according to HCV genotype, and allocated to 1 of 2 subgroups dependent on the achievement of SVR (the SVR (+) and SVR (−)/C0 subgroups) after PEG-IFN/RBV treatment (Fig. 1). The study was approved by the Institutional Review Board of Inha University Hospital, Incheon, South Korea (approval number: INHAUH 2015-11-018).

2.2. Recruitment of clinical database

The following clinical data were obtained at diagnosis of CHC infection in no-treatment group and at time of antiviral therapy in treatment group; age (year), gender, body mass index (BMI, kg/m²), complete blood count, serum alanine aminotransferase (ALT, IU/L) level, prothrombin time (international normalized ratio), serum albumin or bilirubin, serum alpha-fetoprotein (AFP) level, Child-Turcotte-Pugh classification, hepatitis B surface antigen or antibody, HCV RNA (IU/mL), HCV genotype, and presence of LC. LC was clinically diagnosed based on evidence of portal hypertension (encephalopathy, esophageal varices, ascites, or splenomegaly), low platelet count (< 100,000/mm²), or liver ultrasonography (USG) findings. SVR was defined as an undetectable HCV RNA level at 24 weeks later after completing antiviral therapy.

2.3. Surveillance of HCC

Liver USG or computed tomography and serum AFP levels were checked every 6 months for HCC surveillance in study subjects. Follow-up started from the end of antiviral treatment in the treatment group and after diagnosis of CHC infection in the no-treatment group and continued until date of HCC diagnosis or last follow-up.

2.4. Statistical analyses

Patient baseline characteristics are described as medians (ranges) or frequencies. Differences between categorical or continuous variables were analyzed using the Chi-squared test, the Fisher exact test, or the Student t test. Statistical differences among 3 or more groups were analyzed by ANOVA test with Turkey multiple comparison test. Multivariate analysis was conducted using the logistic regression model to identify the independent risk factors of HCC. Odds ratios with 95% confidence intervals were calculated using the logistic regression model. Two-tailed P-values of < 0.05 were considered statistically significant, and the statistical analysis was performed using SPSS v19.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Patient baseline characteristics

A total of 1176 patients were enrolled in the study (Fig. 1); baseline characteristics are summarized in Table 1. Median patient age was 51 years (range, 18–95 years), and 696 (59.2%)
were male. LC was present in 230 (19.6%) patients, and all were in a compensated state. Genotype 1 was the most common (n= 433, 36.8%), and the majority (n= 391, 90.3%) of them were genotype 1b. Median follow-up duration was 31 months (range, 6–144 months). The SVR (+) and SVR (−) subgroups contained 306 and 183 patients, respectively, and the no-treatment group contained 687 patients. One hundred thirty-nine (55.4%) and 141 (71.9%) of genotype 1 (n=687 patients. One hundred thirty-nine (55.4%) and 141 (71.9%) of genotype 1 (n=687 patients. One hundred thirty-nine (55.4%) and 141 (71.9%) of genotype 1 (n=687 patients.

### Table 1
Baseline characteristics of the patients.

| Variables                  | All (n = 1176) | SVR (n = 306) | No SVR (n = 183) | No treatment (n = 687) | P value |
|----------------------------|----------------|---------------|------------------|------------------------|---------|
| Age, y                     | 51 (18–95)     | 44 (21–89)º  | 49 (24–79)³      | 57 (18–95)³            | <0.01†  |
| Gender (male), n (%)       | 696 (59.2)     | 198 (64.7)    | 117 (63.9)       | 381 (55.5)             | <0.01†  |
| BMI, kg/m²                 | 23.7 (13.9–37.9) | 23.9 (15.8–37.2)² | 24.2 (17.6–37.9)³ | 23.1 (13.9–37.3)³      | <0.01†  |
| Cirrhosis, n (%)           | 230 (19.6)     | 29 (9.5)      | 34 (18.6)        | 167 (24.3)             | <0.01†  |
| ALT, IU/L                 | 54 (6–1118)     | 57 (10–919)²a | 65 (12–987)³b   | 51 (6–1118)⁵           | <0.01†  |
| HCV RNA, IU/mL            | 8.7 × 10⁹ (30–1.3 × 10⁹)³ | 7.7 × 10⁹ (30–8.5 × 10⁹)³ | 8.6 × 10⁹ (472–3.4 × 10⁹)³ | 8.9 × 10⁹ (30–1.3 × 10⁹)³ | 0.68†   |
| HCV genotype, n (%)       | 433 (36.8)     | 139 (45.4)    | 112 (61.2)       | 182 (28.5)             | <0.01†  |
| 1                         | 234 (20.6)     | 141 (46.1)    | 55 (30.1)        | 152 (22.1)             |         |
| Mixed type (1 and 2)      | 4 (0.3)        | 1 (0.3)       | 0 (0)            | 3 (0.4)                |         |
| 3 or 4                    | 5 (0.4)        | 1 (0.3)       | 0 (0)            | 4 (0.5)                |         |
| 6                         | 74 (6.3)       | 24 (7.8)      | 16 (8.7)         | 34 (4.9)               |         |
| No data                   | 312 (26.5)     | 0 (0)         | 0 (0)            | 312 (45.4)             |         |
| Antiviral treatment       |                |               |                  |                        | 0.08⁶   |
| Conventional IFN → PEG-IFN/RBV | 33 (6.7)      | 16 (5.2)   | 17 (9.3)         | NA                     |         |
| PEG-IFN/RBV naive         | 456 (38.3)     | 290 (50.3)    | 168 (90.7)       | NA                     |         |
| FU duration, mo           | 31 (6–144)⁷    | 42 (6–144)⁵   | 52 (6–144)⁶     | 21 (6–144)⁵            | <0.01†  |

ALT = alanine aminotransferase, BMI = body mass index, FU = follow-up, HCV = hepatitis C virus, NA = not available, PEG-IFN/RBV = peg-interferon plus ribavirin, SVR = sustained virologic response.

† Median (range), ANOVA test was used, and the same superscript letter means nonsignificant difference between groups based on Turkey multiple comparison test.

‡ Chi-squared test was used.

† Fisher exact test was used.

Analysis was performed in 489 patients with antiviral treatment.

3.2. Clinical characteristics of patients with or without HCC

Clinical characteristics of patients with or without HCC were analyzed in the treatment and no-treatment groups (Table 2). In the treatment group, median patient age was greater (P < 0.01) and LC was more frequent (P < 0.01) in patients who developed HCC than in those who did not. Other factors, such as, gender,
BMI, ALT, HCV RNA, HCV genotype, and follow-up duration, were similar in these 2 HCC subgroups (P values for all > 0.05) (Table 2). In the no-treatment group, median patient age was greater for those who developed HCC (P < 0.01), males (P= 0.03), and the rate of cirrhosis (P < 0.01) were significantly higher in patients who developed HCC (Table 2).

3.3. Cumulative HCC development in patients with CHC infection

HCC developed in 114 (9.7%) of the 1176 study subjects over a median follow-up of 31 months. The 2-, 4-, and 6-year cumulative HCC development rates of patients in the SVR (+) subgroup (0%, 0%, and 1.1%, respectively) were significantly lower than in the SVR (−) subgroup (3.9%, 6.4%, and 9.8%) and in the no-treatment group (9.7%, 13.0%, and 17.8%) (P values for all < 0.01) (Fig. 2A). The 2-, 4-, and 6-year cumulative HCC development rates of study subjects with LC were significantly greater than those without LC (24.3%, 30.4%, and 38.4% vs 1.3%, 2.3%, and 3.1%, respectively, P < 0.01) (Fig. 2B).

Data for HCV genotypes were available for 864 of the study subjects, and of these, HCC developed in 73 (8.4%) patients. The 2-, 4-, and 6-year cumulative HCC development rates of patients with genotype 1 were significantly greater than those with other genotypes (6.1%, 7.4%, and 10.4% vs 3.2%, 8.1%, and 9.6%, respectively, P= 0.09) (Fig. 2C).

3.4. Cumulative HCC development in patients with CHC with respect to antiviral treatment

In the treatment group, HCC developed in 20 (4.1%) patients during a median follow-up duration of 46 months. In this group, the 2-, 4-, and 6-year cumulative HCC development rates of patients with genotype 1 tended to be greater than those with other genotypes (8.9%, 13.5%, and 19.0% vs 0.6%, 1.4%, and 2.1%, respectively, P < 0.01) (Fig. 3A), and the 2-, 4-, and 6-year cumulative HCC development rates of patients with genotype 1 were significantly greater than those with other genotypes (2.8%, 4.1%, and 6.8% vs 0.4%, 2.1%, and 2.1%, respectively, P= 0.047) (Fig. 3B).

In the no-treatment group, HCC developed in 94 (13.7%) patients during a median follow-up duration of 21 months. In this group, the 2-, 4-, and 6-year cumulative HCC development rates were significantly greater for male than female patients (10.9%, 15.4%, and 20.0% vs 8.4%, 10.0%, and 15.0%, respectively, P= 0.02) (Fig. 4A), and the 2-, 4-, and 6-year cumulative HCC development rates of patients with LC were significantly greater than those of patients without LC (30.5%, 37.1%, and 46.1% vs 2.0%, 3.2%, and 4.1%, respectively, P < 0.01) (Fig. 4B). HCV genotype data were available for 375 patients in the no-treatment group, and HCC developed in 53 (14.1%) of these patients, and the cumulative overall HCC development rates of patients with genotype 1 or other genotypes were similar (P= 0.59) (Fig. 4C).

3.5. Factors predictive of HCC development in all patients with CHC

For all study subjects, univariate analysis showed that older age (hazard ratio [HR] 1.06, P < 0.01), presence of cirrhosis (HR 14.89, P < 0.01), higher serum HCV RNA levels (HR 1.01, P < 0.05), SVR (−) (HR 8.52, P < 0.01), and no antiviral treatment (HR 16.19, P < 0.01) were related to HCC development (Table 3). Multivariate analysis showed that older age (HR 1.03, P < 0.01), presence of cirrhosis (HR 9.92, P < 0.01), SVR (−) (HR 7.02, P < 0.01), and no antiviral treatment (HR 6.76, P < 0.01) independently predicted HCC development (Table 3).

3.6. Factors predictive of HCC development in patients with CHC based on antiviral treatment

Significant predictive factors of HCC development in the treatment and no-treatment groups were shown in Table 4. In the treatment group, older age (HR 1.05, P = 0.02), presence of cirrhosis (HR 6.35, P < 0.01), and SVR (−) (HR 10.73, P < 0.01) independently predicted HCC development (Table 4). In the
no-treatment group, older age (HR 1.03, \( P < 0.01 \)), male (HR 1.68, \( P = 0.02 \)), and presence of cirrhosis (HR 11.64, \( P < 0.01 \)) independently predicted HCC development (Table 4).

4. Discussion

In the present study, HCC occurred in 9.7% of all 1176 study subjects over a median follow-up of 31 months. In the treatment group, the 6-year cumulative HCC development rates were 1.1% and 9.8% in the SVR (+) and SVR (−) subgroups, respectively, and in the no-treatment group, the 6-year cumulative HCC development rate was substantially higher at 17.8%. Furthermore, among all study subjects, the risk of HCC development was significantly greater for older patients, in those with cirrhosis, in those who did not achieve SVR on PEG-IFN/RBV, and in those in the no-treatment group. Interestingly, older age, presence of cirrhosis, and failure to achieve SVR were found to independently predict HCC development even among patients in the treatment group.

In the present study, the risk of HCC development was significantly higher in the SVR (−) than in the SVR (+) subgroup, which occurs with previous results.\(^{10–13}\) This suggests that increasing SVR rates reduce HCC development risk in patients with CHC. In fact, SVR rates for genotypes 1 and 2 in the treatment group of the present study were as low as 55.4% and 71.9%, respectively. However, recently recommended first-line antiviral regimens, such as, sofosbuvir-based or daclatasvir/asunaprevir-based regimens, in the treatment-naïve CHC patients have reported to have SVR rates of up to 98% to 100% in treatment-naïve CHC genotype 1 patients with treatment durations as short as 12 or 24 weeks.\(^{7,9,24}\) Moreover, in genotype 2 patients, sofosbuvir-based regimens have been reported to have high SVR rates of more than 95%.\(^{7,9,25}\) Although long-term treatment outcomes, such as, HCC development rates

Figure 3. HCC development in patients who received antiviral treatment. The cumulative HCC development rate of patients with LC was significantly greater than that of those without LC (\( P < 0.01 \)) (A). The cumulative HCC development rate of patients with genotype 1 was significantly greater than that of those with other genotypes (\( P = 0.047 \)) (B). HCC = hepatocellular carcinoma, LC = liver cirrhosis.

Figure 4. HCC development in patients who did not receive antiviral treatment. The cumulative HCC development rate of male patients was significantly greater than that of female patients (\( P = 0.02 \)) (A). The cumulative HCC development rate of patients with LC was significantly greater than that of those without LC (\( P < 0.01 \)) (B). The cumulative overall HCC development rate of patients with genotype 1 or another genotype were similar (\( P = 0.59 \)) (C). HCC = hepatocellular carcinoma, LC = liver cirrhosis.
have not been reported for these new drugs, it can be expected that 
the higher SVR rates achieved will be reflected by decrease in HCC 
development rates. Therefore, active antiviral therapy based on 
these new regimens needs to be considered to achieve high SVR 
rates in patients with treatment-naive CHC. 

Many patients on the PEG-IFN/RBV regimen experience side 
effects, and as a result, about 10% to 20% and 20% to 30% of 
those discontinue treatment or continue at reduced dosages, 
respectively.[26,27] However, new DAA agents have fewer side 
effects, and as a result, about 10% to 20% and 20% to 30% of 
those discontinue treatment or continue at reduced dosages, 
respectively.[26,27] In a previous study, we 
found that 27.4% (n=181) of patients treated with PEG-IFN/ 
RBV were nonadherent due to dose reduction and drug 
discontinuation in 45.3% and 54.7%, respectively.[31] In the 
present study, 37.4% of patients in the treatment group failed to 
achieve SVR, and this was found to be an independent risk factor 
of HCC development in patients with CHC. Although incidences 
of antiviral therapy discontinuation were not evaluated, the side 
effects of PEG-IFN/RBV are a probably an important cause of 
discontinuation, and thus, of treatment failure. Currently, 
patients with CHC who failed to achieve SVR on PEG-IFN/ 
RBV can be retreated with new DAA agents and expected to 
achieve high SVR rates of 90% to 95%.[7–9] Accordingly, 
accumulating evidence suggests the risk of HCC development in 
patients with CHC who failed to achieve SVR on PEG-IFN/RBV 
may be reduced by retreatment with new DAA agents. 

Several factors are considered contraindications to the PEG- 
IFN/RBV regimen.[11] Historically, older patients with CHC have 
been excluded from clinical trials using IFN-based regimens due 
to drug toxicities, and an advanced age has been considered as 
major limitation to IFN-based anti-HCV therapy for reasons of 
poor tolerability and response.[12–14] Thus, anti-HCV therapy for 
older patients constitutes a major unmet need. On the other hand, 
new era of DAA regimen, such as, sofosbuvir- and daclatasvir/ 
asunaprevir-based regimens, have no such contraindications, 
because the incidences of side effects are considerably lower. 
[25,35,36] Accordingly, because an advanced age is a risk factor 
of HCC development in patients with CHC and new DAA agents

### Table 3

Significant predictive factors of HCC development in patients with chronic HCV infection.

| Variables                  | Univariate analysis |          |          |          | Multivariate analysis |          |          |
|----------------------------|---------------------|----------|----------|----------|-----------------------|----------|----------|
|                            | HR                  | 95% CI   | P        | HR       | 95% CI                | P        |          |
| Age, y                     | 1.06                | 1.04–1.07 | <0.01    | 1.03     | 1.02–1.05             | <0.01    |          |
| Gender, male               | 1.35                | 0.92–1.99 | 0.13     | —        | —                     | —        |          |
| BMI, kg/m²                 | 1.01                | 0.95–1.06 | 0.87     | —        | —                     | —        |          |
| Cirrhosis (presence)       | 14.89               | 9.41–23.56| <0.01    | 9.92     | 6.22–15.83            | <0.01    |          |
| ALT, IU/L                  | 0.99                | 0.99–1.01 | 0.21     | —        | —                     | —        |          |
| HCV RNA, IU/mL             | 1.01                | 1.00–1.01 | 0.03     | 1.00     | 1.00–1.01             | 0.37     |          |
| HCV genotype               |                     |          |          |          |                      |          |          |
| 1 vs others                | 1.51                | 0.94–2.44 | 0.09     | —        | —                     | —        |          |
| Antiviral treatment        |                     |          |          |          |                      |          |          |
| SVR (+) (reference)        | 8.52                | 2.51–28.96| <0.01    | 7.02     | 2.06–23.87            | <0.01    |          |
| No treatment               | 16.19               | 5.12–51.15| <0.01    | 6.76     | 2.10–21.71            | <0.01    |          |

**Subjects:** n=1176; event, HCC development during follow-up period (n=114).

**ALT** = alanine aminotransferase, **BMI** = body mass index, **HCC** = hepatocellular carcinoma, **HCV** = hepatitis C virus, **HR** = hazard ratio, **SVR** = sustained virologic response.

† Cox-proportional hazards model with backward elimination method.

Analysis was performed for 864 patients whose data for HCV genotype could be available.

### Table 4

Significant predictive factors of HCC development in chronically HCV-infected patients with or without antiviral treatment.

| Variables                  | Antiviral treatment (n=489) |          |          |          | No antiviral treatment (n=687) |          |          |
|----------------------------|----------------------------|----------|----------|----------|-------------------------------|----------|----------|
|                            | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |          |          |
|                            | HR                  | 95% CI   | P        | HR       | 95% CI                | P        |          |
| Age, y                     | 1.07                | 1.03–1.11 | <0.01    | 1.04     | 1.03–1.06              | <0.01    |          |
| Gender, male               | 1.03                | 1.41–2.28 | 0.95     | —        | —                     | —        |          |
| BMI, kg/m²                 | 1.06                | 0.95–1.19 | 0.30     | —        | —                     | —        |          |
| Cirrhosis (presence)       | 8.85                | 3.61–21.73| <0.01    | 14.28    | 8.21–24.84             | <0.01    |          |
| ALT, IU/L                  | 0.99                | 0.99–1.01 | 0.64     | —        | —                     | —        |          |
| HCV RNA, IU/mL             | 1.00                | 1.00–1.01 | 0.23     | —        | —                     | —        |          |
| HCV genotype               |                     |          |          |          |                      |          |          |
| 1 vs others                | 2.69                | 0.97–7.41 | 0.06     | —        | —                     | —        |          |
| Antiviral response         |                     |          |          |          |                      |          |          |
| SVR (+) vs SVR (+)          | 12.38               | 2.87–53.54| <0.01    | 10.73    | 2.49–46.33             | <0.01    |          |

**ALT** = alanine aminotransferase, BMI = body mass index, CI = confidence interval, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, NA = not available, SVR = sustained virologic response.

† Cox-proportional hazards model with backward elimination method.

Analysis was performed for 375 patients whose data for HCV genotype could be available.
are well tolerated, advanced age should not be contraindicate to active antiviral treatment.

In HCC, carcinogenesis is a multistep process, although the mechanism involved has yet to be elucidated. Nonetheless, LC is a well-known risk factor of HCC development regardless of underlying liver disease, and thus, cirrhotic patients are candidates for active surveillance program of HCC development.[137] In addition, cirrhotic patients with HBV infection have been actively treated with antiviral drugs.[138] Although the previous guideline recommended cirrhotic patients with HCV infection can be treated using PEG-IFN/RBV, it is also stated that suitable patients should have compensated liver function and acceptable hematological indices.[139] Furthermore, PEG-IFN/RBV has been frequently related to hematologic abnormalities, such as, neutropenia, anemia, and thrombocytopenia, and as shown in our previous study, about 5% of patients experienced severe hematologic side effects.[29,30,31]

On the other hand, recently recommended DAA agents have been associated with grade 3 or 4 hematologic abnormalities in fewer than 1% of treated patients.[28,32,33,34] In addition, according to current guidelines, HCV patients with decompensated cirrhosis can also be treated with new DAA agents,[35,36] and in the present study, multivariate analysis showed that LC was an independent risk factor of HCC development in patients with CHC regardless of PEG-IFN/RBV therapy. The above-mentioned evidence strongly suggests that cirrhotic patients with CHC need to be actively treated with highly active oral DAA agents to reduce the risk of HCC development. Although recent studies reported that HCC recurrence has been unexpectedly higher in patients with CHC who receiving DAAAs, they were retrospective studies, and enrolled patients were not randomized.[39,40] Furthermore, in the other prospective study, there was no evidence of high HCC recurrence in patients with HCV after DAAAs.[41] Therefore, the results of these retrospective studies may not reduce the significance of the present study.

Several limitations of the present study require consideration. First, selection bias could not be avoided because of the retrospective design of the study. Second, histologic differences in liver tissues could have confounded our analysis of factors associated with HCC development. However, liver tissue samples could not be obtained from enrolled subjects because biopsy is not a mandatory before the initiation of anti-HCV therapy. Third, some factors potentially associated with the risk of HCV-related HCC, such as, obesity, diabetes mellitus, and insulin resistance, were not addressed in the present study. Fourth, median follow-up duration was relatively short as 31 months, and therefore, long-term follow-up data are needed. Fifth, our recommendation regarding the need for active antiviral therapy based on new DAA agents in patients with CHC with some risk factors was made based on results obtained for PEG-IFN/RBV therapy. Because of time limitations imposed by the recent introduction of the new DAA agents, the preventive effects of these drugs on HCC development in patients with CHC needs further detailed evaluation in the future.

Summarizing, the present study shows that the risk of HCC development in CHC is significantly higher for patients with an advanced age, those with cirrhosis, those who have failed to achieve SVR, and those not treated with PEG-IFN/RBV. In particular, it was found for patients with CHC treated with PEG-IFN/RBV, an older age, presence of cirrhosis, and failure to achieve SVR independently predicted HCC development, and in patients with treatment-naïve CHC, an older age, a male gender, and presence of cirrhosis were found to predict HCC development. In our opinion, patients with CHC with one of these factors should be viewed as candidates for active antiviral therapy in the new era of highly effective oral antiviral drugs.

References

[1] Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335-74.
[2] Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5:538–67.
[3] 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 randomised trial. Lancet 2001; 358:958–65.
[4] Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–82.
[5] Khuroo MS, Khuroo NS, Dahab ST. Meta-analysis: a randomized trial of peginterferon plus ribavirin for the initial treatment of chronic hepatitis C genotype 4. Aliment Pharmacol Ther 2004;20:931–8.
[6] Nguyen MH, Trinh HN, Garcia R, et al. Higher rate of sustained virologic response in chronic hepatitis C genotype 6 treated with 48 weeks versus 24 weeks of peginterferon plus ribavirin. Am J Gastroenterol 2008;103:1131–5.
[7] Panel AIH. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015;62:932–54.
[8] European Association for Study of LiverEASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol 2014;60:392–420.
[9] Korean Association for the Study of the LiverKASL clinical practice guidelines: management of hepatitis C. Clin Mol Hepatol 2016;22:76–99.
[10] Moon C, Jung KS, Kim do Y, et al. Lower incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. J Viral Hepat 2006;13:409–14.
[11] Bruno S, Strollofoli T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology 2007;45:579–87.
[12] Yoshida H, Shiraatori Y, Moriyama M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy, Ann Intern Med 1999;131:174–81.
[13] Nishiguchi S, Kuroki T, Nakatani S, et al. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 1995;346:1051–5.
[14] Kasahara A, Hayashi N, Mochizuki K, et al. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Osaka Liver Disease Study Group. Hepatology 1998;27:1394–402.
[15] Toyoda H, Kumada T, Tada T, et al. Risk factors of hepatocellular carcinoma development in non-cirrhotic patients with sustained virologic response for chronic hepatitis C virus infection. J Gastroenterol Hepatol 2013;30:1183–9.
[16] Moon C, Jung KS, Kim do Y, et al. Lower incidence of hepatocellular carcinoma and cirrhosis in hepatitis C patients with sustained virological response by pegylated interferon and ribavirin. Dig Dis Sci 2015;60:573–81.
[17] Honda T, Ishigami M, Masuda H, et al. Effect of peginterferon alfa-2b and ribavirin on hepatocellular carcinoma prevention in older patients with chronic hepatitis C. J Gastroenterol Hepatol 2015;30:521–8.
[18] Lee SS, Jeong SH, Jang ES, et al. Prospective cohort study on the outcomes of hepatitis C virus-related cirrhosis in South Korea. J Gastroenterol Hepatol 2015;30:1281–7.
[19] Ogawa E, Furusyo N, Kajiwara E, et al. Efficacy of pegylated interferon alpha-2b and ribavirin treatment on the risk of hepatocellular carcinoma in patients with chronic hepatitis C: a prospective, multicenter study. J Hepatol 2013;58:495–501.
[20] Fernandez-Rodriguez CM, Alonso S, Martinez SM, et al. Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: outcomes and factors predicting response. Am J Gastroenterol 2010;105:2164–72.
[21] Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol 2010;52:623–7.

[22] Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996;111:1018–22.

[23] Di Lelio A, Cestari C, Lomazzi A, et al. Cirrhosis: diagnosis with sonographic study of the liver surface. Radiology 1989;172:389–92.

[24] Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889–98.

[25] Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878–87.

[26] Fried MW. Side effects of therapy of hepatitis C and their management. Hepatology 2002;36:5237–44.

[27] Russo MW, Fried MW. Side effects of therapy for chronic hepatitis C. Gastroenterology 2003;124:1711–9.

[28] Manns M, Pol S, Jacobson IM, et al. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet 2014;384:1597–605.

[29] Capraru CI, Kuczynski M, La D, et al. Efficacy and safety of sofosbuvir plus simeprevir in patients with advanced HCV cirrhosis. Hepatology 2014;60:665a.

[30] Gonzalez GR, Gonzalez SA, Nazario HE, et al. Efficacy of Ledipasvir plus Sofosbuvir with or without ribavirin in hepatitis C genotype 1 patients who failed previous treatment with Simeprevir plus Sofosbuvir. Hepatology 2015;62:775a.

[31] Jin YJ, Lee JW, Lee JI, et al. Multicenter comparison of PEG-IFN alpha2a or alpha2b plus ribavirin for treatment-naive HCV patient in Korean population. BMC Gastroenterol 2013;13:74.

[32] Honda T, Katano Y, Shimizu J, et al. Efficacy of peginterferon-alpha-2b plus ribavirin in patients aged 65 years and older with chronic hepatitis C. Liver Int 2010;30:527–37.

[33] Thabut D, Le Calvez S, Thibault V, et al. Hepatitis C in 6,865 patients 65 yr or older: a severe and neglected curable disease? Am J Gastroenterol 2006;101:1260–7.

[34] Szabo S, Rheem J, Sundaram V. Hepatitis C infection in the elderly. Dig Dis Sci 2015;60:3170–80.

[35] Modi AA, Nazario H, Trotter JF, et al. Safety and efficacy of simeprevir plus sofosbuvir with or without ribavirin in patients with decompensated genotype 1 hepatitis C cirrhosis. Liver Transplant 2016;22:281–6.

[36] Moreno C, Lasser L, Delwaide J, et al. Sofosbuvir in combination with simeprevir is an effective and well-tolerated treatment option for previously treated chronic hepatitis C patients with advanced fibrosis or cirrhosis: real-life experience from Belgium. Hepatology 2015;62:746a.

[37] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–2.

[38] Terrault NA, Brouwer NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261–83.

[39] Conn F, Buonfili F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016;65:727–33.

[40] Reig M, Marino Z, Perello C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016;65:719–26.

[41] ANRS Collaborative Study Group on Hepatocellular Carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT Cohorts). Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: data from three ANRS cohorts. J Hepatol 2016;65:734–40.