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

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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, DAA = 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.[1] 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.[10–15] 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[18,20,21] 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 DAAs 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.

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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 history of 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 (−) 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/m^2), 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/mm^3), or liver ultrasonography (USG) findings.[22,23] 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%)

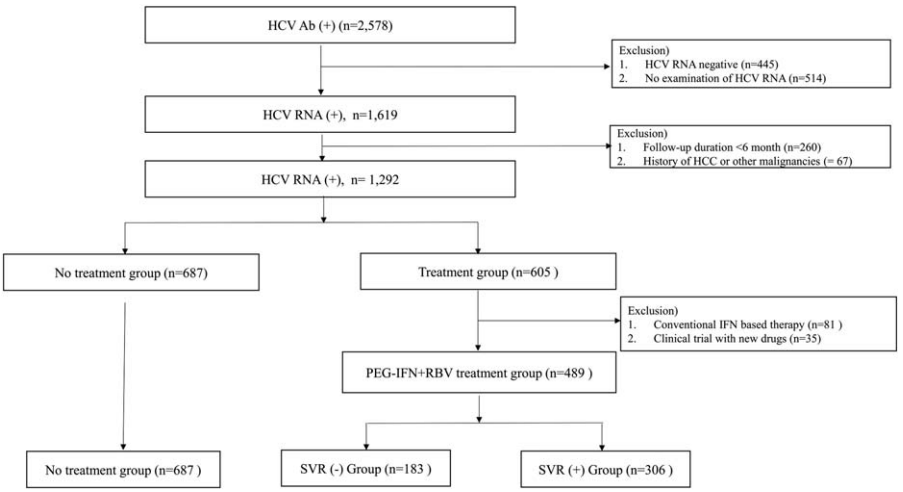

Figure 1. Study subjects. A total of 1176 patients were enrolled in the present study. Of these, 306 and 183 patients were allocated to SVR (+) and SVR (−) subgroups, respectively, and 687 patients were allocated to the no-treatment group. SVR = sustained virologic response.

Table 1

Baseline characteristics of the patients.

Variables	All (n = 1176)	Antiviral treatment (n = 489)		No treatment (n = 687)	*P* value
		SVR (n = 306)	No SVR (n = 183)		
Age*, y	51 (18–95)	44 (21–80)[a]	49 (24–79)[b]	57 (18–95)[c]	<0.01†
Gender (male), n (%)	696 (59.2)	198 (64.7)	117 (63.9)	381 (55.5)	<0.01‡
BMI*, kg/m^2	23.7 (13.9–37.9)	23.9 (15.8–37.2)[a]	24.2 (17.6–37.9)[a]	23.1 (13.9–37.3)[b]	<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)[a]	65 (12–987)[a,b]	51 (6–1118)[b]	<0.01†
HCV RNA*, IU/mL	8.7×10^5 ($30–1.3 \times 10^8$)	7.7×10^5 ($30–8.5 \times 10^7$)[a]	8.6×10^5 ($472–3.4 \times 10^7$)[a]	8.9×10^5 ($30–1.3 \times 10^8$)[a]	0.68†
HCV genotype, n (%)					<0.01§
1	433 (36.8)	139 (45.4)	112 (61.2)	182 (26.5)	
2	348 (29.6)	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					0.08‡,‖
Conventional IFN → PEG-IFN/RBV	33 (6.7)	16 (5.2)	17 (9.3)	NA	
PEG-IFN/RBV naive	456 (93.3)	290 (94.8)	166 (90.7)	NA	
FU duration*, mo	31 (6–144)	42 (6–144)[a]	52 (6–144)[b]	21 (6–144)[c]	<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.

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 = 251) and 2 (n = 196) patients administered PEG-IFN/RBV achieved SVR, respectively. In the treatment group, there were 456 (93.3%) treatment naïve patients. Median age was greater and the frequency of LC was higher in the no-treatment group than in the treatment group or the 2 SVR subgroups, respectively (Table 1).

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,

Table 2

Comparison of clinical characteristics of the patients with or without HCC during follow-up.

Variables	Antiviral treatment (n = 489)			No treatment (n = 687)		
	HCC (n = 20)	No HCC (n = 469)	*P* value†	HCC (n = 94)	No HCC (n = 593)	*P* value†
Age*, y	58 (42–71)	45 (21–80)	<0.01	71 (44–91)	54 (19–95)	<0.01
Gender (male), n (%)	13 (65.0)	302 (64.4)	1.00	62 (66.0)	319 (53.8)	0.03
BMI*, kg/m^2	25 (21–30)	24 (16–38)	0.08	24 (14–31)	23 (14–37)	0.30
Cirrhosis, n (%)	12 (60.0)	51 (10.9)	<0.01	79 (84.0)	88 (14.8)	<0.01
ALT*, IU/L	67 (31–223)	60 (10–987)	0.45	57 (12–460)	50 (6–1118)	0.61
HCV RNA*, IU/mL	7.9×10^5 ($472–5.1 \times 10^6$)	8.2×10^5 ($30–8.5 \times 10^7$)	0.67	6.4×10^5 ($30–8.9 \times 10^5$)	5.9×10^5 ($40–1.3 \times 10^8$)	0.54
HCV genotype, n (%)			0.17‡			0.08‡
1	15 (75.0)	236 (50.3)		31 (33.0)	151 (25.5)	
2	5 (25.0)	191 (40.7)		19 (20.2)	133 (22.4)	
Mixed type (1 and 2)	0 (0)	1 (0.2)		0 (0)	3 (0.5)	
3 or 4	0 (0)	1 (0.2)		2 (2.1)	2 (0.3)	
6	0 (0)	40 (8.5)		1 (1.1)	33 (5.6)	
No data	0 (0)	0 (0)		41 (43.6)	271 (45.7)	
FU duration*, mo	44 (6–144)	46 (6–144)	0.95	15 (6–144)	22 (6–144)	0.32

ALT = alanine aminotransferase, BMI = body mass index, FU = follow-up, HCC = hepatocellular carcinoma, HCV = hepatitis C virus.

* Median (range).

† Chi-squared test or Student *t* test was used to compare between 2 groups.

‡ Fisher exact test was used.

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 tended to be 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 LC were significantly greater than those without LC (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, $P = 0.03$), 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

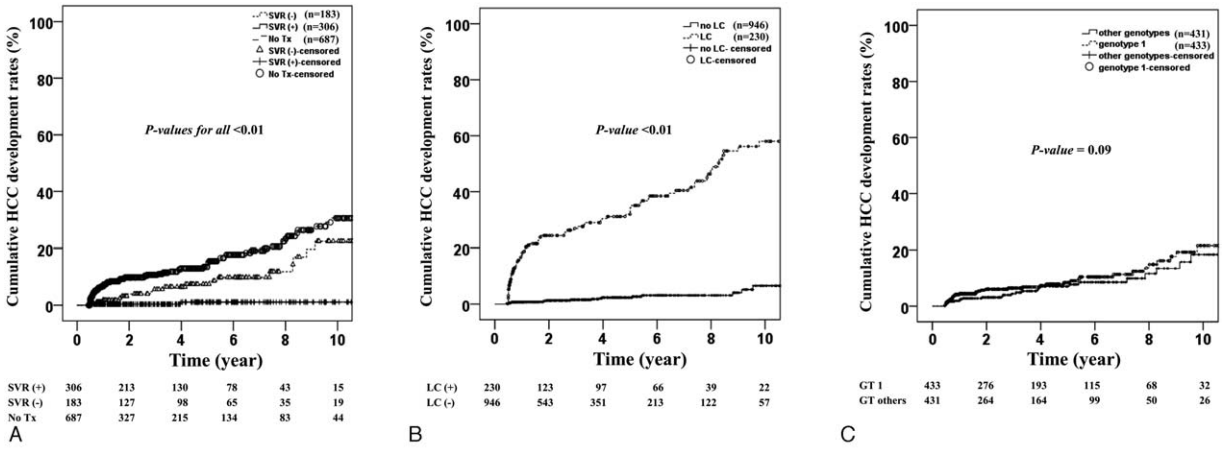

Figure 2. HCC development in all study subjects. The cumulative HCC development rate of patients who achieved SVR on PEG-IFN/RBV therapy was significantly lower than the rate of those who did not and than that of those not treated with PEG-IFN/RBV (P values for all < 0.01) (A). The cumulative HCC development rate of study subjects with LC was significantly greater than those without LC ($P < 0.01$) (B). The cumulative HCC development rate of study subjects with genotype 1 was not significantly greater than those with other genotypes ($P = 0.09$) (C). HCC = hepatocellular carcinoma, LC = liver cirrhosis, PEG-IFN/RBV = peg-interferon plus ribavirin, SVR = sustained virologic response.

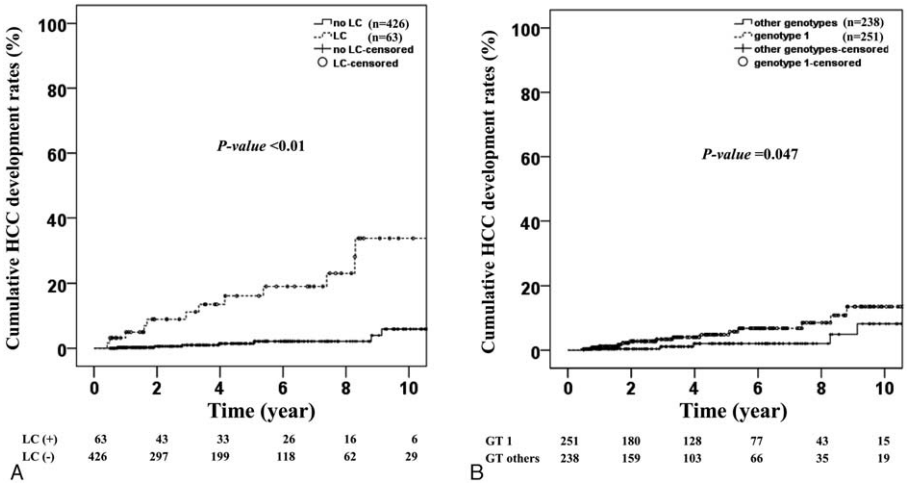

Figure 3. HCC development in patients who received antiviral treatment. The cumulative HCC development rate of patients with LC was significantly greater than that of those without LC ($P < 0.01$) (A). The cumulative HCC development rate of patients with genotype 1 was significantly greater than that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

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.[10–15] 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 a 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

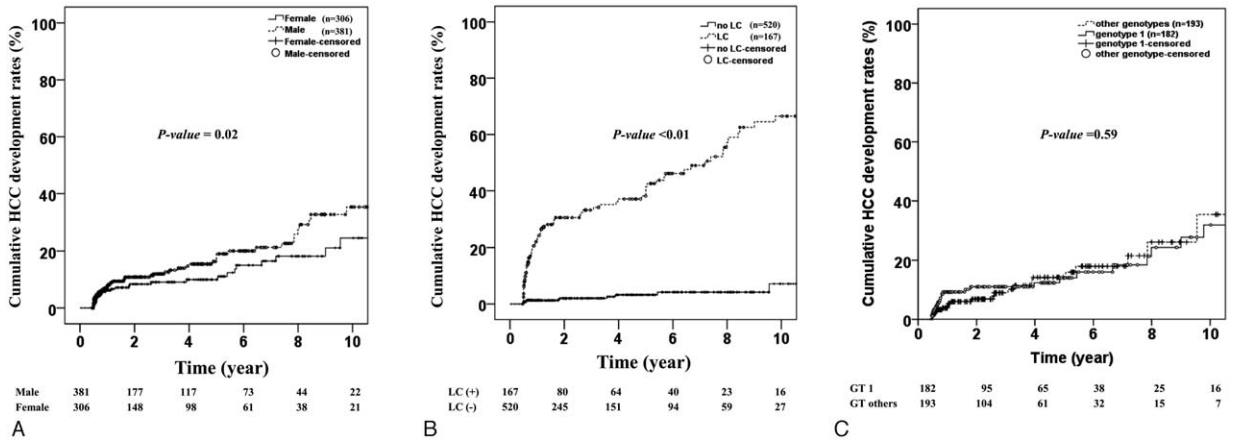

Figure 4. HCC development in patients who did not receive antiviral treatment. The cumulative HCC development rate of male patients was significantly greater than that of female patients ($P = 0.02$) (A). The cumulative HCC development rate of patients with LC was significantly greater than that of those 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.

Table 3

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

	Univariate analysis			Multivariate analysis*		
Variables	**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/m^2	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)						
SVR (−)	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, CI = confidence interval, 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.

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-naïve 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, are better tolerated, and have higher compliance rates than the PEG-IFN/RBV regimen.[28–30] 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.[1] 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.[32–34] 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 4

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

	Antiviral treatment (n = 489)						No antiviral treatment (n = 687)					
	Univariate analysis			Multivariate analysis*			Univariate analysis			Multivariate analysis*		
Variables	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age, y	1.07	1.03–1.11	<0.01	1.05	1.01–1.09	0.02	1.04	1.03–1.06	<0.01	1.03	1.02–1.05	<0.01
Gender, male	1.03	1.41–2.28	0.95	—	—	—	1.64	1.07–2.52	0.02	1.68	1.08–2.59	0.02
BMI, kg/m^2	1.06	0.95–1.19	0.30	—	—	—	1.03	0.97–1.09	0.36	—	—	—
Cirrhosis (presence)	8.85	3.61–21.73	<0.01	6.35	2.55–15.80	<0.01	14.28	8.21–24.84	<0.01	11.64	6.68–20.29	<0.01
ALT, IU/L	0.99	0.99–1.01	0.64	—	—	—	0.99	0.99–1.00	0.49	—	—	—
HCV RNA, IU/mL	1.00	1.00–1.01	0.23	—	—	—	1.00	1.00–1.01	0.13	—	—	—
HCV genotype												
1 vs others	2.69	0.97–7.41	0.06	—	—	—	1.21	0.69–0.21	0.50†	—	—	—
Antiviral response												
SVR (−) vs SVR (+)	12.38	2.87–53.54	<0.01	10.73	2.49–46.33	<0.01	NA	NA	NA	NA	NA	NA

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.[37] In addition, cirrhotic patients with HBV infection have been actively treated with antiviral drugs.[38] 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.[1] 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.[29–31]

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.[28–30,35,36] In addition, according to current guidelines, HCV patients with decompensated cirrhosis can also be treated with new DAA agents,[7–9] 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 DAAs, 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 DAAs.[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.

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