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The clinical outcomes of chronic hepatitis C in South Korea

A prospective, multicenter cohort study

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Abstract

This prospective cohort study aimed to elucidate the clinical outcome and its related factors of chronic hepatitis C in a hepatitis B-dominant Asian region.

From January 2007 to October 2012, 382 patients with chronic hepatitis C without liver cirrhosis were prospectively enrolled at 6 university hospitals, and regularly followed until Apr 2014 to identify the development of liver cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), and overall survival.

During the median follow-up of 39.0 months (range 18.0–81.0 months), liver cirrhosis, hepatic decompensation, and HCC developed in 42 patients (11.0%), 4 patients (1.0%), and 12 patients (3.1%), respectively. The cumulative probability of development of cirrhosis at 3 years and at 5 years was 9.6% and 16.7%, respectively. That of HCC at 3 and 5 years was 1.6% and 4.5%, respectively. The 3-year and 5-year overall survival rate was 99.7% and 96.0%, respectively. Pegylated interferon-based antiviral therapy was undertaken in 237 patients (62.0%) with a sustained virologic response (SVR) rate of 74.3%. The factors related to the overall clinical outcomes were age ≥55 years (HR 2.924, $P=0.016$), platelet counts $<150 \times 10^9$/L (HR 3.195, $P=0.007$), and the achievement of SVR (HR 0.254, $P=0.002$).

The clinical outcomes of this Korean chronic hepatitis C cohort were modest with minimal mortality, but significant disease progression occurred in the patients with old age, low platelet, and non-SVR after interferon-based antiviral treatment or no treatment, suggesting priority for direct acting antiviral therapy.

Abbreviations: AFP = alpha-fetoprotein, ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, DAA = direct acting antiviral therapy, EVR = early virologic response, FIB-4 index = fibrosis-4 index, GGT = gamma glutamyltransferase, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HCV RNA = hepatitis C virus ribonucleic acid, HR = hazard ratio, INR = international normalized ratio, pegIFN-α = pegylated interferon alpha, PR = pegIFN- α and ribavirin, RVR = rapid virologic response, SVR = sustained virologic response.

Keywords: hepatitis C virus, hepatocellular carcinoma, liver cirrhosis, survival, sustained virologic response

1. Introduction

The global prevalence of hepatitis C virus (HCV) infection has increased from 2.3% to 2.8% between 1990 and 2005.[1] An estimate of the prevalence of anti-HCV among Koreans adults over 20 years old was 0.78% in 2009, and 10% to 15% of HCC is attributable to HCV infection in Korea.[2,3] Although the natural history of HCV infection is highly variable according to study population and method, an estimated 15% to 30% of chronic hepatitis patients have progression to cirrhosis over the ensuing 3 decades.[4,5] Therefore, HCV infection is the leading cause of liver cirrhosis and hepatocellular carcinoma (HCC) resulting in a major global health burden.[6]

Antiviral therapy with pegylated interferon alpha (pegIFN-α) and ribavirin (PR therapy) was the standard of care for all HCV genotypes during the last decade.[7–9] Thus, clinical outcomes rather than the natural history of chronic hepatitis C are recently

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reported including the risk of HCC development and overall mortality with various rates of antiviral treatment.[10–14] A clinical outcome study is important in the era of direct acting antiviral therapy (DAA), because the high cost of drugs can be justified by cost-effectiveness based on the clinical outcomes, especially in many resource-constrained regions. Several studies, performed mostly in Western countries, predicted that HCV-related morbidity and mortality may increase in the next decade, even though DAA is available.[15–17] However, very little is known about the clinical outcomes of chronic hepatitis C in East Asian countries where hepatitis B virus (HBV) is prevalent rather than HCV.[7–9] Moreover, the epidemiological features and host genetic background of chronic hepatitis C patients in the Asian region are different from those of Western countries.[18]

A prospective, multicenter HCV cohort in South Korea was established and its cohort profile was reported previously.[19] Using those cohort data, this study aimed to elucidate the incidence of liver cirrhosis, HCC, and all-cause mortality in chronic hepatitis C patients, and to identify the risk factors related to those clinical outcomes. To the best of our knowledge, this is the first prospective cohort study in a real-world clinical practice that observed the major outcomes of chronic hepatitis C patients in an HBV-prevalent Asian region.

2. Materials and methods

2.1. Study design and patients

In the prospective, multicenter Korea HCV cohort, 1065 patients with HCV ribonucleic acid (RNA) positivity >6 months were enrolled at 6 university hospitals from January 2007 to October 2012. Among them, 378 patients who were initially given diagnose of liver cirrhosis or HCC, 154 patients who had previously received antiviral therapy before enrollment, and 151 patients followed less than 18 months, were excluded from this study. Therefore, 382 treatment-naive, chronic hepatitis C patients who were followed >18 months were the subjects of this study. Patients coinfected with HBV, defined as hepatitis B surface antigen (HBsAg) positivity, were included, because coinfection with HBV and HCV may have a significant impact on the clinical outcomes of HCV in HBV-endemic areas. All patients provided written informed consent, and the study was approved by the Institutional Review Board of each hospital. The study protocol was consistent with the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Questionnaire survey and clinical data collection at enrollment

At enrollment, a trained research coordinator at each hospital interviewed the patient using a standardized questionnaire, which included socio-demographics (age, gender, education, and occupation), health behavior (smoking and drinking), accompanying diseases (cancer, psychiatric disease, diabetes, kidney disease, cerebro-, and cardiovascular diseases), and their lifetime experience with theoretical risk factors for HCV infection (blood transfusion, hemodialysis, intravenous drug use, tattooing, piercing, needle stick injury, acupuncture, dental procedures, diagnostic endoscopy, surgery, family history of HCV-related liver disease, and number of sexual partners).

Each subject underwent blood biochemical tests such as serum HCV RNA level, HCV genotype, HBsAg, anti-hepatitis B virus surface antibody (anti-HBs), complete blood cell count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, gamma glutamyl transferase (GGT), albumin, creatinine, and alpha fetoprotein (AFP), and radiological examinations such as ultrasonography or computed tomography (CT). Completed questionnaires and clinical data were collected and entered into the electronic case report form (CRF) at the Korean HCV cohort study group homepage (http://www.hcvcohort.or.kr).

2.3. Follow-up and determination of clinical outcomes

The subject patients were prospectively followed at least every 6 months at each institution by medical examinations or phone call until April 2014. The median follow-up duration was 39.0 months (range 18.0–81.0). Standard antiviral therapy with pegIFN-α and ribavirin was administered to the patients in whom it was indicated according to the attending physicians' decision at each site. During the study period, no DAA was available in Korea except in clinical trial settings, and 28 patients participated in the clinical trials including 1st generation DAA with PR therapy. Until April 2014, the individual patient's status was determined as remaining as chronic hepatitis, changed to cirrhosis (compensated or decompensated), development of HCC or mortality. Cirrhosis of the liver was defined as histological results in liver biopsy, or compatible radiological findings accompanied by clinical features indicative of portal hypertension, such as thrombocytopenia (a platelet count $< 10^9$/L), gastroesophageal varices, or splenomegaly. HCC was diagnosed by histological examination or by typical radiographic findings consisting of arterial enhancement and venous wash-out on contrast-enhanced (CT) or magnetic resonance imaging (MRI) of hepatic nodules. The composite disease progression was defined as development of liver cirrhosis, hepatic decompensation (ascites, spontaneous bacterial peritonitis, variceal bleeding, and hepatic encephalopathy), HCC, death, or liver transplantation.

As a simple and validated serum marker of hepatic fibrosis, AST-platelet ratio index (APRI) ([AST/upper normal limit] × 100/platelet [10^9/L]) and FIB-4 (age [years] × AST [IU/L]/(platelets [10^9/L] × (ALT [IU/L])$^{1/2}$) were calculated for each patient at enrollment and at last follow-up. As an indirect marker of fibrosis progression, the change of FIB-4 index/year (delta FIB-4) was calculated, in which delta FIB-4 was calculated as [(FIB-4 at last follow-up) – (FIB-4 at enrollment)]/follow-up years.

2.4. Statistical analysis

Categorical variables were compared with the χ^2 test, and continuous variables were compared with Student t test. The cumulative incidence rates of liver cirrhosis, HCC, all-cause mortality, and composite disease progression were calculated and plotted using the Kaplan–Meier method. Differences of the incidence rate between subgroups were analyzed using the log-rank test. To identify the factors associated with disease progression, multivariate analysis was performed using Cox regression analysis for variables with P values of <0.05 on the univariate analysis. A P value of <0.05 was considered to indicate a statistically significant difference. SPSS version 21.0 (IBM SPSS Inc, Chicago, IL) was used for all statistical analyses except incidence rate analysis, for which STATA 13 (StataCorp LP, College Station, TX) was used.

3. Results

3.1. Patient characteristics and antiviral treatment

Baseline characteristics of the 382 patients with chronic hepatitis C are summarized in Table 1, showing a mean age of 54.8 years,

Table 1

Comparison of clinical features between treated group and nontreated group using pegylated interferon and ribavirin therapy in chronic hepatitis C patients.

Variables	Total n = 382 (%)	Treated group n = 237 (%)	Nontreated group n = 145 (%)	*P* value
Age at entry, y†	54.8 ± 12.7	50.6 ± 10.8	61.6 ± 12.5	<0.001*
Male‡	166 (43.5)	105 (44.3)	61 (42.1)	0.669
BMI (kg/m^2)†	23.3 ± 3.9	23.2 ± 4.0	23.5 ± 3.7	0.473
Obesity (BMI >25 kg/m^2)‡	110 (29.6)	64 (29.1)	46 (30.5)	0.776
Current alcohol intake‡	131 (37.8)	96 (44.9)	35 (26.3)	0.001*
Alcohol intake amount‡				0.042*
<20 g/d	279 (79.5)	165 (76.0)	114 (85.1)	
≥20 g/d	72 (20.5)	52 (24.0)	20 (14.9)	
Current smoker at enrollment‡	127 (37.0)	87 (41.4)	40 (3.1)	0.034*
Smoking amount‡				0.020*
<20 pack-years	266 (80.4)	165 (81.3)	101 (78.9)	
≥20 pack-years	65 (19.6)	38 (18.7)	27 (21.1)	
Employed state‡	181 (50.0)	125 (56.3)	56 (40.0)	0.003*
Follow-up duration, months				
Mean ± SD†	41.9 ± 16.2	38.8 ± 17.1	38.6 ± 16.5	0.761
Median (range)	39.0 (18.0–81.0)	39.0 (18–81)	39.0 (18–80)	0.710
Diabetes mellitus‡	52 (13.9)	29 (12.2)	22 (15.3)	0.398
Serologic findings				
HBV coinfection‡	13 (3.9)	10 (4.7)	3 (2.4)	0.387
HCV RNA titer >400,000 IU/mL‡	220 (60.9)	140 (61.1)	80 (60.6)	0.921
HCV genotype‡				0.133
1	179 (51.0)	109 (48.2)	70 (56.0)	
2	164 (46.7)	111 (49.1)	53 (42.4)	
3/4/6	2 (0.6)/1 (0.3)/5 (1.4)	1 (0.8)/0 /1 (0.8)	1 (0.4)/1 (0.4)/4 (1.8)	
Laboratory findings				
Platelet (×10^9/L)†	188.4 ± 60.9	188.6 ± 61.3	188.0 ± 60.4	0.938
AST (IU/L)†	78.0 ± 141.3	81.2 ± 114.0	72.6 ± 177.2	0.562
ALT (IU/L)†	103.8 ± 303.9	102.6 ± 146.5	105.8 ± 456.3	0.921
GGT (IU/L)†	69.4 ± 86.2	72.5 ± 84.6	64.5 ± 88.7	0.442
Total bilirubin (mg/dL)†	0.88 ± 0.53	0.85 ± 0.37	0.93 ± 0.72	0.228
Albumin (g/dL)†	4.25 ± 0.37	4.27 ± 0.36	4.20 ± 0.39	0.077
Prothrombin time, INR†	1.23 ± 4.87	1.38 ± 6.07	0.96 ± 0.39	0.508
AFP (ng/mL)†	6.97 ± 10.85	7.78 ± 13.12	5.93 ± 6.81	0.169
APRI†	1.24 ± 2.92	1.27 ± 2.12	1.20 ± 3.88	0.825
FIB-4 index‡	2.68 ± 1.90			0.017*
<1.45	118 (31.9)	81 (35.5)	37 (26.1)	
1.45–3.25	131 (40.4)	89 (39.0)	54 (38.0)	
>3.25	109 (29.5)	58 (25.4)	51 (35.9)	
ΔFIB-4 index/y†	−0.05 ± 0.98	−0.27 ± 0.99	0.35 ± 0.82	<0.001*
Liver biopsy performed‡	69 (18.1)	62 (26.2)	7 (4.8)	<0.001*
Potential Risk factors for HCV infection				
Intravenous drug use‡	27 (7.2)	18 (7.8)	9 (6.3)	0.582
Transfusion before screening‡	106 (31.3)	60 (27.9)	46 (37.1)	0.079
Needle stick injury‡	33 (9.9)	21 (10.3)	12 (9.3)	0.757
Tattooing‡	163 (43.5)	103 (44.4)	60 (42.0)	0.644
Piercing‡	151 (40.2)	103 (44.4)	48 (33.3)	0.033*
Operation history‡	180 (48.0)	108 (46.6)	72 (50.3)	0.475
No. of sexual partners ≥3‡	48 (16.4)	28 (16.4)	20 (16.4)	0.997
Treatment regimen				
Pegylated interferon alpha and ribavirin (PR) combination‡		209 (88.2)		
Clinical trial including PR‡		28 (11.8)		
SVR‡		168 (74.3)		
RVR‡		129 (64.2)		
EVR (complete/partial)‡		177 (81.2)		
Relapse‡		19 (5.0)		

P values are for the comparison between groups.

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, BMI = body mass index, EVR = early virologic response, FIB-4 index = fibrosis-4 index, GGT = gamma glutamyltransferase, HBV = hepatitis B virus, HCV = hepatitis C virus, INR = international normalized ratio, PR = pegylated interferon alpha and ribavirin combination therapy with standard duration of treatment according to HCV genotype or on-treatment response, RNA = ribonucleic acid, RVR = rapid virologic response, SVR = sustained virologic response.

* $P < 0.05$.

† Mean ± standard deviation.

‡ n (percent).

and male gender in 43.5%. Mean follow-up duration was 41.9 months. In total, 179 patients (51.0%) were infected with genotype 1 HCV, and 164 (46.7%) were infected with genotype 2. The mean ALT level was 103.8 IU/L, and the mean albumin level was 4.25 g/dL. Liver biopsy was performed only in 18.1% of the subjects, and our diagnostic criteria for liver cirrhosis was a clinical one with no available liver elastography results. The mean APRI was 1.24, and the mean FIB-4 index was 2.68. A FIB-4 index higher than 3.25 indicating advanced fibrosis (a Metavir fibrosis stage of F3 to F4) was found in 29.5% of the patients at enrollment. HBV coinfection was found in 3.9%, which was similar to that of the general population in South Korea.

A total 237 patients (62.0%) underwent antiviral treatment consisting of pegIFN-α and ribavirin combination as the standard PR therapy (n=209), or clinical trials including 1st generation DAA, in addition to PR therapy (n=28). Sustained virologic response (SVR) was achieved in 168 patients (74.3%) among the 237 treated patients. The achievement rates of SVR in genotype 1 and the other genotype were 64.2% and 85.5%, respectively ($P<0.001$). The SVR rate of the patients with PR therapy was 78.9%, and that of the patients participating in clinical trials was 83.3% ($P=0.655$, unpublished data). The comparative analysis of clinical features between 237 patients who received antiviral treatment and 145 patients who did not undertake the therapy is summarized in Table 1. The treated group showed significantly younger patients with a higher proportion of current alcohol drinkers, current smokers, in an employed state, and in a lower range of FIB-4 index. Liver biopsy was more frequently performed in the treated group than the nontreated group. Interestingly, the mean delta FIB-4/year during the study period was −0.27 in the treated group, while it was +0.35 in the nontreated group.

3.2. Incidence of liver cirrhosis, HCC, and mortality in chronic hepatitis C patients

Of the 382 patients, 42 (11.0%) patients developed liver cirrhosis during the mean follow-up period of 41.9 months. The estimated incidence of cirrhosis development was 33 per 1000 person-years (95% CI, 24.9–45.6). The cumulative probability of development of cirrhosis at 3 years and at 5 years was 9.6% and 16.7%, respectively. None progressed to decompensated cirrhosis as the first clinical event.

HCC developed in 12 patients (3.1%), and the estimated incidence rate of HCC was 9.2 (95% CI, 5.2–16.1) per 1000 person-years for chronic hepatitis patients. The cumulative probability of HCC development at 3 and 5 years was 1.6% and 4.5%, respectively (Fig. 1A). The estimated annual incidence of HCC development was 0.9% in the first 5 years from entry.

Composite disease progression occurred in 50 patients (13.1%); 42 patients developed compensated cirrhosis, 12 patients developed HCC, and 4 patients died. The estimated incidence of the composite disease progression was 40.6 (95% CI, 30.8–53.6) per 1000 person-years for chronic hepatitis C

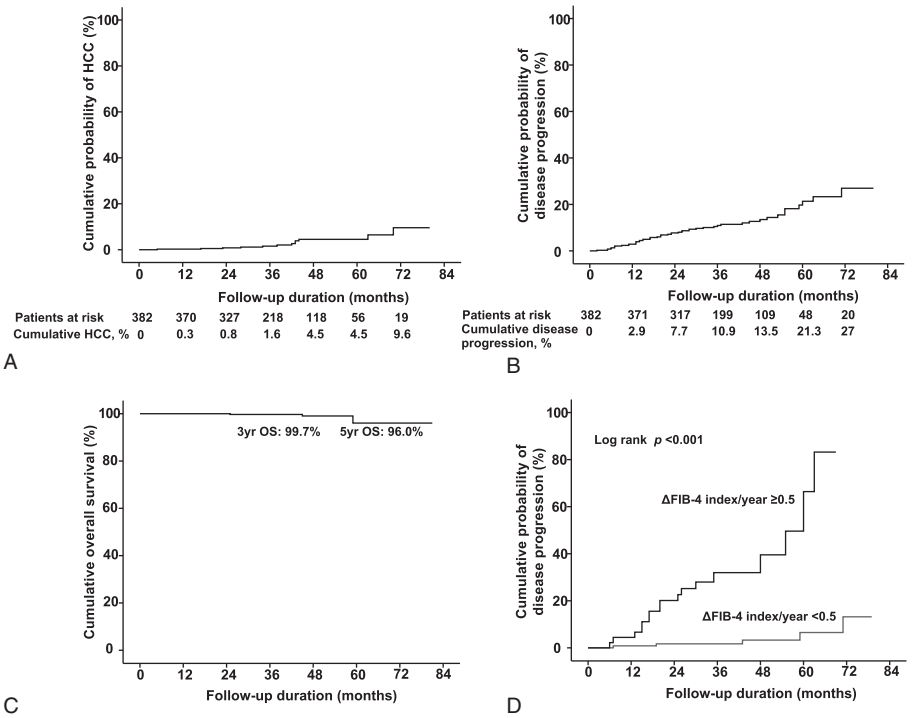

Figure 1. Cumulative probability of development of hepatocellular carcinoma (HCC), composite disease progression, and overall survival. We prospectively observed 382 patients with chronic hepatitis C during the median follow-up period of 39 months to determine the development of HCC, and composite disease progression defined as cirrhosis, decompensation, HCC and mortality, as well as overall survival. (A) HCC developed in 12 patients (3.1%), and the estimated incidence rate of HCC was 9.2 (95% CI, 5.2–16.1) per 1000 person-years for CHC patients. Cumulative probability of HCC development at 3 and 5 years was 1.6% and 4.5%, respectively. (B) The composite disease progression occurred in 50 patients (13.1%); 42 patients developed compensated cirrhosis, 12 patients developed HCC, and 4 patients died. Cumulative probability of disease progression at 3 and 5 years was 10.9% and 21.3% respectively. (C) There were 4 cases of mortality (1.0%) during the follow-up period, due to HCC progression in 1, and extrahepatic causes in the remaining 3 patients. (D) Cumulative probability of overall survival was 99.7% and 96% at 3 and 5 years, respectively. Comparison of cumulative probability of disease progression between delta (Δ) FIB-4 index/year <0.5 and ≥0.5 using the mean value as cutoff in the increased ΔFIB-4 index/year group. ΔFIB-4 index was calculated as the FIB-4 index at the last follow-up minus the FIB-4 index at enrollment.

patients. The cumulative probabilities of the composite disease progression at 3 and 5 years were 10.9% and 21.3%, respectively (Fig. 1B). The estimated annual incidence of the composite disease progression was 4.2%.

There were 4 cases of mortality (1.0%) during the follow-up period. The cause of death was HCC progression in 1 case, and extrahepatic causes in the other 3 cases (cerebral infarction, traumatic subdural hemorrhage, and lung cancer). There were no patients who received liver transplantation. The estimated incidence rate of overall mortality was 3.0 (95% CI, 1.1–7.9) per 1000 person-years. The cumulative probability of overall survival was 99.7% and 96% at 3 and 5 years (Fig. 1C).

3.3. Factors associated with development of HCC and composite disease progression

The univariate analysis of the factors related to HCC development showed that current alcohol intake, platelet count, serum level of albumin, GGT and AFP level, and achievement of SVR were significant factors. On multivariate analysis, albumin ≥3.5 g/dL (hazard ratio [HR] = 0.061, 95% CI = 0.006–0.595, $P = 0.016$) and the achievement of SVR (HR = 0.061, CI = 0.007–0.510, $P = 0.010$) were independent factors for HCC development (Table 2).

The univariate analysis of the composite disease progression showed that age, employment state, diabetes, albumin, GGT, platelet count, achievement of SVR, and FIB-4 score were significantly related factors. Of these, age <55 years (HR = 0.269, 95% CI = 0.142–0.821, $P = 0.016$), high (≥150 × 10^9/L) platelet count (HR = 0.313, CI = 0.134–0.733, $P = 0.007$) and the achievement of SVR (HR = 0.254, CI = 0.108–0.593, $P = 0.002$) were independent factors for the composite disease progression on multivariate analysis (Table 3).

According to antiviral treatment and SVR status, the probability of composite disease progression and HCC development are shown in Fig. 2. The poorest outcome was in the group of patients who failed virologic clearance after antiviral therapy (non-SVR group), followed by the group of treatment-naive

Table 2

Univariate and multivariate analysis of factors associated with HCC development.

	Univariate analysis†		Multivariate analysis†	
Variable	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age at entry, y				
<55				
≥55	3.395 (0.847–11.638)	0.065		
Gender				
Female				
Male	0.565 (0.179–1.781)	0.330		
BMI				
<25 kg/m^2				
≥25 kg/m^2	1.899 (0.602–5.987)	0.274		
Alcohol intake				
No or former				
Current	4.382 (1.130–16.99)	0.033*		
Smoking				
No or former				
Yes	0.625 (0.128–3.047)	0.561		
Diabetes				
No				
Yes	0.910 (0.240–5.020)	0.904		
HCV genotype				
Non-1				
1	3.791 (0.818–17.57)	0.089		
Albumin				
<3.5 g/dL				
≥3.5 g/dL	0.120 (0.015–0.976)	0.047*	0.061 (0.006–0.595)	0.016*
GGT				
<70 IU/L				
≥ 70 IU/L	0.153 (0.035–0.661)	0.012*		
Platelet				
<150 (×10^9/L)				
≥150 (×10^9/L)	0.206 (0.060–0.708)	0.012*		
AFP				
<7 ng/mL				
≥7 ng/mL	7.442 (1.842–30.06)	0.005*		
SVR				
(−)				
(+)	0.054 (0.006–0.448)	0.007*	0.061 (0.007–0.510)	0.010*

P values are for the comparison between groups.

AFP = alpha-fetoprotein, BMI = body mass index, GGT = gamma glutamyl transferase, HCV = hepatitis C virus, SVR = sustained virologic response.

* $P < 0.05$.

† According to the Cox proportional hazard model.

Table 3

Univariate and multivariate analysis of factors associated with the composite disease progression (development of cirrhosis, HCC, or mortality).

	Univariate analysis†		Multivariate analysis†	
Variable	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age at entry, y				
<55				
≥55	3.712 (1.938–7.109)	0.001*	2.924 (1.218–7.021)	0.016*
Gender				
Female				
Male	1.437 (0.825–2.504)	0.200		
BMI				
<25 kg/m^2				
≥25 kg/m^2	1.718 (0.962–3.069)	1.718		
Employed state				
Employed				
Unemployed	2.267 (1.187–4.330)	0.013*		
Alcohol intake				
No or former				
Current	0.874 (0.459–1.663)	0.682		
Smoking				
No or former				
Yes	0.740 (0.379–1.447)	0.379		
Diabetes				
No				
Yes	2.281 (1.212–4.294)	0.011*		
Albumin				
<3.5 g/dL				
≥3.5 g/dL	0.208 (0.064–0.676)	<0.009*		
GGT				
<70 IU/L				
≥70 IU/L	0.490 (0.241–0.996)	0.049*		
Platelet				
<150 (×10^9/L)				
≥150 (×10^9/L)	0.197 (0.108–0.358)	<0.001*	0.313 (0.134–0.733)	0.007*
SVR				
(−)				
(+)	0.233 (0.103–0.525)	<0.001*	0.254 (0.108–0.593)	0.002*
FIB-4 index				
<1.45				
≥1.45	38.35 (2.982–506.26)	0.005*		

P values are for the comparison between groups.

BMI = body mass index, FIB-4 index = fibrosis-4 index, GGT = gamma glutamyl transferase, SVR = sustained virologic response.

* $P<0.05$.

† According to the Cox proportional hazard model.

patients (naive group), while the best outcome was seen in the group of patients who achieved SVR (SVR group).

4. Discussion

This prospective study demonstrated clinical outcomes of chronic hepatitis C in a Korean cohort for the first time. The 5-year overall survival rate of 382 chronic hepatitis C patients was 96%, and the liver-related death occurred in only 1 of 4 mortality cases. The cumulative probability of HCC development at 3 and 5 years was 1.6% and 4.5%, respectively. The cumulative probability of the composite disease progression including development of liver cirrhosis, HCC, and mortality at 3 and 5 years was 10.9% and 21.3%, respectively. The independent factors related to the composite disease progression were age ≥55 years, platelet counts $< 150 \times 10^9$/L, and failure to achieve SVR. Antiviral treatment, mainly PR therapy, was undertaken in 237 patients (62.0%), and SVR was achieved in 168 patients among the 237 treated patients (74.3%). The treated group was younger and had a lower range of FIB-4 index than the nontreated group. Interestingly, the SVR group showed the best outcome compared with both the non-SVR group and the treatment-naive group.

HCC is a major clinical outcome of chronic HCV infection. A posttransfusion chronic hepatitis C cohort from Japan (n = 469) followed from 1989 to 2000 showed a HCC development rate of 11% during a mean 7.7 years of observation (5-year cumulative probability of HCC development, 5.2%).[10] Among them, 145 patients received interferon therapy and 42 patients (29%) achieved sustained response. In the recent study of the Veterans Affairs (VA) clinical registry of the United States from 1999 to 2010, the cumulative probability of HCC development was 3.5% at a mean postindex period of 6.1 years in HCV-infected veterans (n = 128,481).[12] Among them, 24.3% of patients underwent antiviral treatment, and 16.4% of treated patients achieved an undetectable viral load. Our results showed that the cumulative probability of HCC development at 3 and 5 years was 1.6% and

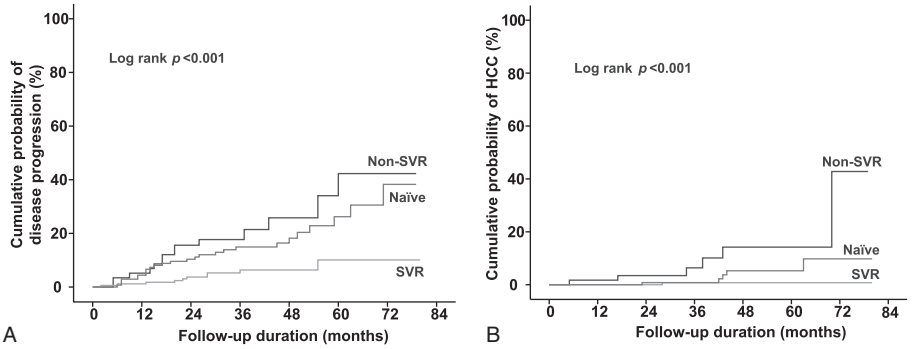

Figure 2. Comparison of cumulative probability of disease progression and of development of hepatocellular carcinoma (HCC) among treatment-naive patients, patients with SVR, and those with non-SVR after pegylated interferon-based antiviral treatment in patients with chronic hepatitis C. (A) Comparison of cumulative probability of composite disease progression among the treatment naive group, SVR-achieved group, and SVR-failed group in patients who underwent antiviral treatment. Composite disease progression is defined as development of cirrhosis, HCC, or mortality. SVR, sustained virologic response was defined as no detectable HCV RNA after 24 weeks of completion of antiviral therapy. (B) Comparison of cumulative probability of HCC among the treatment naive group, SVR-achieved group and SVR-failed group in patients who underwent antiviral treatment.

4.5%, respectively. Considering the high treatment rate and high SVR rate of this study, HCC development seems to be higher than in the US study, but similar to or rather higher than the remote Japanese posttransfusion cohort results. Though the study populations were heterogeneous, and study methods differed greatly from studies on the clinical outcomes of chronic hepatitis C, Korean patients seem to be at higher risk of HCC development than Caucasian patients, due to unknown reasons. The independent factors related to HCC development were lower albumin level and non-SVR in this study, which reflects advanced fibrosis and no viral eradication, respectively.

This study demonstrated that the cumulative probability of overall survival was 99.7% and 96% at 3 and 5 years and the estimated incidence rate of overall mortality was 3.0 (95% CI, 1.1–7.9) per 1000 person-years. Among 4 cases of mortality (1.0%) during the follow-up period, only 1 liver-related death due to HCC progression was observed. Therefore, almost all of the chronic hepatitis C patients did not die due to liver problems within about 5 years of observation. A community-based prospective cohort study from Taiwan reported that 677 HCV RNA-positive people showed significantly higher cumulative probability of all-cause mortality (30.1%) and liver cancer mortality (10.4%) at 18 years of observation than in 298 anti-HCV positive but HCV RNA negative people (12.8% and 1.6%, respectively).[11] The German HCV 1b contaminated anti-D cohort study at 35 years of follow-up (n=718) showed that cirrhosis developed in 9.3% of the overall cohort, with higher incidence in the non-SVR group (15.3%) and treatment naive patients (14.2%) than the SVR group (6%).[14] In the German cohort, including 189 spontaneously recovered HCV infections, 4.2% of patients died (n=30), and cirrhosis-related death was observed in 17 patients. However, the recent VA registry study (n=128,769) showed mortality of 12.0% at a mean postindex period of 6.1 years, which seems to be higher than our results, though the cause of death was not reported in that study.[12] As indicated in the Taiwan, German, and VA registry studies, the clinical outcomes of chronic hepatitis C were quite variable according the study populations, observational period, or method, resulting in difficulty in making a direct comparison of those studies.

A large variety of environmental and host factors related to the disease progression were reported such as age, gender, duration of infection, age at infection, host interleukin 28B polymorphism, alcohol intake, obesity, diabetes, coinfection with hepatitis B virus, or human immunodeficiency virus antiviral treatment or SVR.[20–24] Despite significant heterogeneity, patient's age, fibrosis degree, and SVR were the most commonly reported predictors for disease progression. In this study, the independent factors related to the composite disease progression were age ≥55 years, platelet counts $<150 \times 10^9$/L, and failure to achieve SVR, which were compatible with the previous results. Interestingly, treatment naive patients showed a poor outcome, similar to that of the non-SVR group, compared with the SVR group. The treatment naive group showed older age, lower employment rate, and higher FIB-4 index, suggesting a large proportion of unmet needs for interferon-based therapy.

FIB-4 index was a simple, accurate, and inexpensive method for assessing liver fibrosis in HCV infection, as was demonstrated by the fact that liver biopsy could be avoided in 71% of HIV/HCV coinfection using the FIB-4 index.[25,26] According to the changing speed of the FIB-4 index, as indicated by ΔFIB-4 index/y with a cutoff level of 0.5, the disease progression rates were significantly different. Therefore, during patient follow-up, calculation of ΔFIB-4/yr is meaningful to assess disease progression rate.

Compared with the outcomes of HCV-related liver disease, chronic hepatitis B in Korea resulted in the development of liver cirrhosis at a rate of 5.1% per year (5-year cumulative probability of 23%) and of HCC with 0.8% per year (5-year cumulative probability of 3%).[27,28] The epidemiology of HBV infection and patient demographics of HBV-infected patients are significantly different from those of HCV-infected patients, but the outcomes and liver disease progression rates seem to be not so different.[29] However, due to the intrinsically different characteristics of HBV and HCV disease, head-to-head comparison is of moot value.

There are several limitations of this study. Compared to Western data, the sample size is small, information on alcohol intake and smoking reflected only a 1-year period at enrollment rather than lifetime exposure, the infection period was not known in most of the patients, and follow-up duration was relatively short. However, this is a prospective, multicenter cohort study maintained in a systematic way in real-world practice in HBV endemic Asian chronic hepatitis C patients with extensive clinical data and detailed analysis. This study can provide baseline data

of clinical outcomes in the pre-DAA era, to estimate the additional effects of DAA therapy on the clinical outcomes of chronic hepatitis C in the future.

In conclusion, the clinical outcomes of chronic hepatitis C patients in South Korea were modest but significant with the cumulative probability of development of HCC, and all-cause mortality at 5 years was 4.5% and 4%, respectively. In spite of the relatively high rate of interferon-based antiviral treatment and the high SVR rate, patients with old age, low platelet count, and treatment-naive or nonachievement of SVR should be carefully monitored for disease progression. In these cases, DAA therapy is a top priority.

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