ORIGINAL ARTICLE

Gut and Liver, Vol. 14, No. 2, March 2020, pp. 207-217

Epidemiological and Clinical Characteristics of Hepatitis C Virus Infection in South Korea from 2007 to 2017: A Prospective Multicenter Cohort Study

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See editorial on page 148.

Background/Aims: This study aimed to elucidate the epidemiological and clinical characteristics of chronic hepatitis C (CHC) patients in South Korea from 2007 to 2017 and to compare the treatment patterns between two periods before and after the first approval of direct-acting antivirals (DAA) in South Korea in 2015. **Methods:** This prospective, multicenter cohort enrolled 2,758 patients with hepatitis C virus (HCV) viremia at seven tertiary centers, and clinical data were prospectively collected with questionnaire surveys focused on lifetime risk factors related to HCV infection. **Results:** The HCV patients had a mean age of 57.3 years (50.8% male). Among them, 14.3% showed a positive history of transfusion before HCV screening and 5.6% reported intravenous drug use (IVDU), with significant differences in these risk factors between men and women. The proportions of patients with chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) were 69.5%, 18.9%, and 11.5%, respectively. The mean alanine aminotransaminase level was within the upper normal limit at 49.9%, and the major genotypes were 1b (48.2%) and 2 (46.4%). The overall treatment rate was 53.8%, showing a rapid transition from interferon-based therapy to DAA therapy. In the post-DAA-approval era, the untreated group was older, had a higher prevalence of HCC, and had less education than the treated group. **Conclusions:** More than 90% of CHC patients were over 40 years old, the major genotypes were 1b and 2, and IVDU was observed in less than 6% of CHC patients. Approximately half of the patients underwent antiviral therapy even in the DAA era, showing an unmet need with regard to HCV elimination. **(Gut Liver 2020;14:207-217)**

Key Words: Hepatitis C virus; Epidemiology; Cohort study; Therapeutics; Carcinoma, hepatocellular

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of acute and chronic hepatitis leading to liver cirrhosis and hepatocellular carcinoma (HCC).[1] Globally, 71 million people are living with chronic HCV infection, and approximately 399,000 people died due to HCV in 2015.[2] Though an effective HCV vaccine has not been developed, HCV screening of transfusion blood products significantly reduced the HCV infection rate. However, intravenous drug use (IVDU) and the re-use of needles in healthcare or cosmetics settings are the major transmission routes of HCV infection currently.[3,4]

Since the first generation of direct-acting antivirals (DAA) such as boceprevir and telaprevir were approved in 2011, the development of highly efficacious all-oral DAA combined therapeutics with an excellent safety profile brought about remarkable success in HCV treatments.[5] This success led to the vision of HCV elimination by the World Health Organization, which targets 90% of chronic hepatitis C diagnosed, 80% of eligible

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Received on January 3, 2019. Revised on March 6, 2019. Accepted on April 14, 2019. Published online September 19, 2019.
pISSN 1976-2283 eISSN 2005-1212 https://doi.org/10.5009/gnl19005
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patients treated, and a 65% reduction in the number of HCV deaths by 2030.[6]

However, HCV epidemiology and the disease burden differ greatly around the world depending on the region. For example, IVDU is the major risk factor among Western patients, but HCV contamination in healthcare or cosmetics settings is more common in Asian regions, including South Korea.[7] The distribution of the HCV genotype is geographically diverse, which could result in different clinical outcomes and therapeutic plans. Moreover, HCV infection screening practices and access to DAA therapies vary widely among countries.[8] Therefore, regional data on the epidemiological and clinical characteristics are essential to develop effective strategies by which to prevent HCV and for the active detection of those infected with HCV and the successful delivery of DAA therapies to them. This study aimed to elucidate the epidemiological and clinical characteristics of chronic hepatitis C patients in South Korea from 2007 to 2017 and to investigate the treatment patterns in the two periods before and after the first approval of DAA in South Korea in 2015.

MATERIALS AND METHODS

1. Study design and patients

The Korea HCV cohort is a prospective, multicenter cohort which enrolled 2,910 adult patients who showed positive anti-HCV antibody (anti-HCV) results at seven tertiary centers nationwide from January of 2007 to December of 2017. Among them, 2,758 patients with HCV viremia for more than 6 months were the subjects of this study. The inclusion and exclusion criteria of the subjects are summarized in Fig. 1. The study protocol was approved by the Institutional Review Board of each hospital, and each enrolled patient provided informed written consent.

A questionnaire survey on lifetime exposure to risk factors related to HCV infection was carried out upon enrollment, and clinical data were collected at baseline and at follow-up visits. The patients were prospectively followed every 3 to 12 months according to their physicians' decisions. If patients were lost to follow-up for more than 6 to 12 months, research coordinators at the associated hospital contacted the patients to confirm their clinical status and to encourage a follow-up visit. During a mean follow-up of 8.67 years, 71.7% of the subjects remained in the cohort until December of 2017.

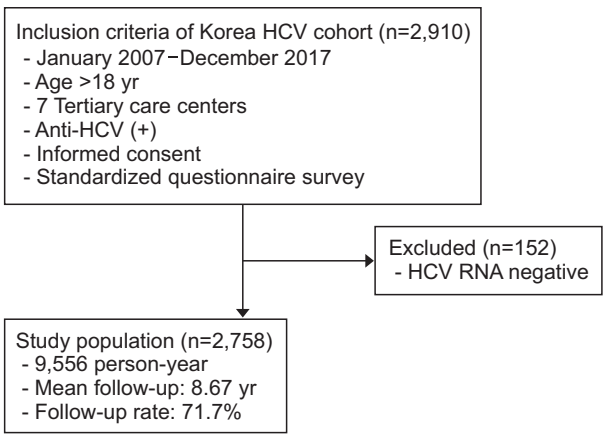

Fig. 1. Inclusion and exclusion criteria for the subjects. In total, 2,910 hepatitis C virus (HCV) cohort patients were identified, of whom 152 did not meet the inclusion criteria. Ultimately, 2,758 patients were analyzed in this study.

Upon the initial enrollment, the subjects were classified into three diagnostic groups according to the severity of liver disease: chronic hepatitis C, liver cirrhosis, and HCC. If a patient was diagnosed as HCC with underlying cirrhosis, he or she was placed into the HCC group. Diagnostic criteria for liver cirrhosis were based on histological results or on at least one clinical sign of portal hypertension, such as cirrhotic features on radiological images, a platelet count of less than 100,000/mm^3, the presence of ascites, gastroesophageal varices, or hepatic encephalopathy. HCC was diagnosed according to histological findings or typical imaging characteristics as defined in the Korean Liver Cancer Study Group guidelines, which are similar to major international guidelines.[9,10]

2. Data collection and questionnaire survey

Upon enrollment of the cohort, trained research coordinators in seven hospitals interviewed the patients using a standardized questionnaire, which included socioeconomic status (age, sex, education level, and occupation), health behaviors (smoking and alcohol drinking), and medical history including comorbidities (other cancers, thyroid disease, psychiatric disease, diabetes, kidney disease, cerebrovascular disease, and cardiovascular disease). Lifetime exposure to possible risk factors for HCV infection were surveyed; these included blood transfusions, IVDU, needle stick injuries, hemodialysis, a diagnosis of hemophilia, dental procedures, endoscopy, acupuncture, surgery, tattooing, piercing, a familial history of HCV-related liver disease, living with HCV carriers, and the number of sexual partners.

Laboratory data were collected from the medical records from the results of tests of anti-HCV, serum HCV RNA levels, HCV genotype, the hepatitis B virus surface antigen (HBsAg), the anti-hepatitis B virus surface antibody, white blood cell counts, hemoglobin levels, platelet counts, aspartate aminotransferase (AST), alanine aminotransaminase (ALT), total bilirubin, gamma glutamyl transferase, albumin, creatinine, and alpha fetoprotein upon the enrollment of each patient. Results of imaging studies such as abdominal ultrasonography or computed tomography, and the results of liver pathology or transient elastography (FibroScan®; Echosens, Paris, France) were collected if available. Detailed information about antiviral treatments, such as the therapeutic regimens, treatment period, and response along with the survival status and disease progression status were obtained. These data were entered into the established electronic case

Table 1. Baseline Clinical Characteristics of the Korea HCV Cohort According to Sex

Variable	Total patients (n=2,758)	Male (n=1,401)	Female (n=1,357)	p-value*
Mean age, yr	57.3±12.9	56.6±13.0	58.0±12.8	0.005
Median age, yr	57 (49–66)	57 (48–66)	58 (50–67)	
Age, yr				<0.001
10–19	13 (0.5)	12 (0.9)	1 (0.1)	
20–29	34 (1.2)	13 (0.9)	21 (1.6)	
30–39	187 (6.8)	95 (6.8)	92 (6.8)	
40–49	512 (18.7)	313 (22.5)	199 (14.8)	
50–59	784 (28.6)	362 (26.0)	422 (31.3)	
60–69	743 (27.1)	370 (26.5)	373 (27.7)	
≥70	469 (17.1)	229 (16.4)	240 (17.8)	
Education (n=2,692)				
Above high-school level	1,561 (58.0)	907 (66.1)	654 (49.6)	<0.001
Smoking (current or former) (n=2,732)	1,295 (47.4)	1,084 (77.9)	211 (15.7)	<0.001
Alcohol (current or former) (n=2,733)	1,455 (53.2)	1,039 (74.7)	416 (31.0)	<0.001
Asymptomatic at infection (n=1,764)	1,567 (88.8)	780 (89.6)	787 (88.1)	0.343
Diagnostic category				
Chronic hepatitis	1,918 (69.5)	918 (65.5)	1000 (73.7)	<0.001
Liver cirrhosis	522 (18.9)	260 (18.6)	262 (19.3)	
Hepatocellular carcinoma	318 (11.5)	223 (15.9)	95 (7.0)	
Child-Pugh class B or C	146 (7.9)	86 (8.9)	60 (6.8)	0.096
Biochemistry				
ALT >40 IU/L	1,343 (49.4)	772 (55.7)	571 (42.8)	<0.001
AFP >20 IU/mL	325 (16.8)	190 (18.9)	135 (14.4)	0.008
HCV RNA, quantification				
>600,000 IU/mL	1,066 (48.1)	533 (48.6)	533 (47.6)	0.624
>2,000 IU/mL	1,878 (84.7)	924 (84.3)	954 (85.2)	0.568
>1,000 IU/mL	1,906 (86.0)	934 (85.2)	972 (86.8)	0.288
HCV RNA (mean, $\times 10^6$ IU/mL)	2.5±9.8	3.7±10.1	2.4±8.8	0.514
HCV RNA (median, $\times 10^5$ IU/mL)	5.1	5.0	5.1	
HCV genotype (n=2,078)				
Genotype 1/1b	1,088 (52.4)/1,001 (48.2)	585 (56.6)/537 (53.8)	503 (48.2)/464 (46.2)	<0.001
Genotype 2/2a	964 (46.4)/805 (38.8)	430 (41.6)/377 (34.7)	534 (51.1)/428 (39.3)	
History of HCV risk factors				
Intravenous drug use	155 (5.6)	125 (8.9)	30 (2.2)	<0.001
Needle stick injury	189 (6.9)	116 (8.3)	73 (5.4)	0.003
Transfusion before 1995	396 (14.4)	155 (11.1)	241 (17.8)	<0.001
Tattooing	1,031 (37.4)	205 (14.6)	826 (60.9)	<0.001
Piercing	922 (33.4)	100 (7.1)	822 (60.6)	<0.001
Acupuncture	2,243 (81.4)	1,085 (77.4)	1,158 (85.3)	<0.001
Living with HCV carrier	67 (3.2)	36 (3.3)	31 (3.0)	0.727
Hemodialysis	30 (1.1)	17 (1.2)	13 (1.0)	0.518
No. of sexual partner ≥4	453 (18.9)	374 (31.1)	79 (6.6)	<0.001
Dental procedure	2,551 (92.5)	1,281 (91.4)	1,270 (93.6)	0.032
Endoscopy	2,377 (86.2)	1,178 (84.1)	1,199 (88.4)	0.001

Data are presented as mean±SD, median (interquartile range), or number (%).
HCV, hepatitis C virus; ALT, alanine aminotransferase; AFP, alpha fetoprotein.
*Male vs female.

report form on the homepage of the Korean Centers for Disease Control, Korea HCV cohort study (http://is.cdc.go.kr/).

3. Statistical analyses

The baseline demographic and clinical characteristics upon cohort enrollment were descriptively analyzed and compared between two groups of the patients enrolled during the periods before and after the first approval of DAA in South Korea in 2015. Continuous variables are expressed as the mean±standard deviation (SD) or the frequency (percent), and discrete variables are expressed as absolute and relative frequencies. The Student t-test and a one-way analysis of variance were applied to compare continuous data. Categorical variables were compared with the Pearson chi-square tests. The statistical analysis was conducted with SPSS version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Demographic and clinical characteristics of the Korea HCV cohort from 2007 to 2017

This prospective cohort consisted of 2,758 patients with HCV viremia who were enrolled from January of 2007 to December of 2017 with a median follow-up duration of 8.67 years, covering a population of 9,556 person-years. The dropout rate of the cohort due to death, follow-up loss, or withdrawal of consent was 28.3% overall, meaning that 71.7% of the originally enrolled patients remained under continuous follow-up until 2017 (Fig. 1). The number of patients enrolled in the cohort for each year is as follows: 179 (2007), 244 (2008), 235 (2009), 227 (2010), 228 (2011), 233 (2012), 301 (2013), 303 (2014), 234 (2015), 297 (2016), 277 (2017).

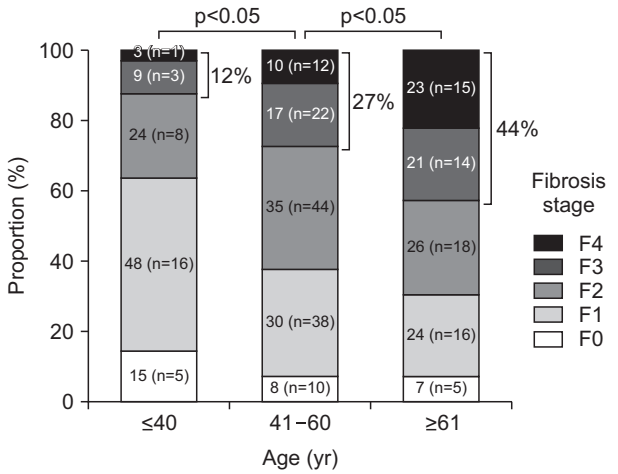

Fig. 2. Distribution of the stages of fibrosis according to liver biopsy stratified by the age group of hepatitis C virus patients. The proportion of those with advanced fibrosis (stages 3 and 4) increased significantly as age increased: 12% at age ≤40 years, 27% at age 41–60 years, and 44% at age ≥61 years (all p<0.05, comparison of the advanced fibrosis proportion F3 and F4).

The demographic and clinical profiles of the entire cohort with comparisons between male and female patients are summarized in Table 1. The mean age of the cohort patients was 57.3 years, those over 40 years accounted for 91.5%, and the male-to-female ratio was 1.03. Among them, 53.2% were current or former alcohol drinkers, 47.4% were current or former smokers, and 58.0% had a high school degree or higher education. Upon the diagnosis of HCV infection, 88.8% of the subjects were asymptomatic.

By diagnostic category, chronic hepatitis, cirrhosis and HCC accounted for 69.5%, 18.9%, and 11.5%, respectively. The mean age of patients with chronic hepatitis (54.9 years), cirrhosis (61.1 years) and HCC (65.4 years) showed a significant increase according to disease progression. Likewise, the proportion of males in the chronic hepatitis (47.9%), liver cirrhosis (49.8%), and HCC (70.1%) groups increased according to disease progression (Supplementary Table 1). The proportion of those with advanced fibrosis (stages 3 and 4) increased significantly according to an increase in age. These rates were 12% at age ≤40 years, 27% at age 41 to 60 years, and 44% at age ≥61 years (Fig. 2). Indirect markers of fibrosis, in this case the AST-to platelet ratio index

Table 2. HCV Genotype Distribution in the Korea HCV Cohort (n=2,078)

Genotype	No. of patients (%)
Genotype 1	
1	36 (1.7)
1a	49 (2.4)
1b	993 (47.8)
1c	10 (0.5)
Subtotal	1,088 (52.4)
Genotype 2	
2	130 (6.3)
2a	380 (18.3)
2b	26 (1.3)
2c	3 (0.1)
2a/c	425 (20.5)
Subtotal	964 (46.4)
Genotype 3	
3	2 (0.1)
3a	11 (0.5)
Subtotal	13 (0.6)
Genotype 4	
4	1 (0.1)
4a	2 (0.1)
Subtotal	3 (0.2)
Genotype 6	
6c	10 (0.5)

HCV, hepatitis C virus.

Table 3. Comparison of Baseline Clinical Characteristics in the Pre- and Post-DAA Approval Periods

Variable	Total patients (n=2,758)	Pre-DAA 2007–2014 (n=1,950)	Post-DAA 2015–2017 (n=808)	p-value*
Age, yr	57.3±12.9	56.15±12.7	60.0±13.6	<0.001
10–19	13 (0.5)	9 (0.5)	4 (0.5)	<0.001
20–29	34 (1.2)	26 (1.3)	8 (1.0)	
30–39	187 (6.8)	161 (8.3)	26 (3.3)	
40–49	513 (18.7)	393 (20.2)	119 (15.0)	
50–59	785 (28.6)	547 (28.1)	237 (29.8)	
60–69	745 (27.1)	508 (26.1)	235 (29.6)	
≥70	469 (17.1)	303 (15.6)	166 (20.9)	
Male sex	1,401 (50.8)	966 (49.5)	435 (53.8)	0.040
Education (n=2,692)				
Above high-school level	1,561 (56.6)	1,145 (60.5)	416 (52.1)	<0.001
Smoking, current/former (n=2,732)	1,295 (47.4)	921 (47.7)	374 (46.7)	0.632
Alcohol, current/former (n=2,733)	1,455 (53.2)	1,047 (54.4)	408 (50.6)	0.069
Diagnostic category				
Chronic hepatitis	1,918 (69.5)	1,359 (69.7)	559 (69.2)	0.032
Liver cirrhosis	522 (18.9)	384 (19.7)	138 (17.1)	
Hepatocellular carcinoma	318 (11.5)	207 (10.6)	111 (13.7)	
Comorbidity				
HBsAg positive (n=1,540)	51 (3.3)	21 (2.1)	30 (5.4)	0.001
Obesity (BMI ≥25/≥30 kg/m^2) (n=2,630)	720 (27.4)/78 (3.0)	520 (27.0)/51 (2.6)	200 (28.5)/27 (3.9)	0.168
Cancer (except HCC)	241 (8.7)	120 (6.2)	121 (15.0)	<0.001
Thyroid disease	88 (3.2)	57 (2.9)	31 (3.8)	0.234
Psychiatric disease	117 (4.2)	84 (4.3)	33 (4.1)	0.791
Cerebrovascular disease	50 (1.8)	32 (1.6)	18 (2.2)	0.293
Cardiovascular disease	710 (25.7)	441 (22.6)	269 (33.3)	<0.001
Kidney disease	38 (1.4)	26 (1.3)	12 (1.5)	0.267
Diabetes	514 (18.6)	349 (17.9)	165 (20.4)	0.121
Basal laboratory findings				
White blood cell, counts/μL	5,250.6±2,079.7	5,181.5±1,980.1	5,423.9±2,302.7	0.012
Hemoglobin, g/dL	13.5±1.9	13.4±1.9	13.6±1.8	0.078
Platelet, ×1,000/μL	165.2±75.1	163.0±71.2	170.8±83.6	0.017
Albumin, g/dL	4.1±0.5	4.1±0.5	4.1±0.5	0.355
Total bilirubin, mg/dL	1.0±2.5	0.9±0.7	1.1±4.6	0.442
GGT, IU/L	78.2±118.9	76.4±115.7	82.4±126.1	0.278
Creatinine, mg/dL	1.02±1.2	1.0±1.3	0.9±1.0	0.036
ALT, IU/L				0.005
<1× UNL	1,377 (49.9)	942 (48.7)	435 (55.5)	
1–2× UNL	730 (26.5)	538 (27.8)	192 (24.5)	
2–5× UNL	476 (17.3)	347 (17.9)	129 (16.5)	
>5× UNL	137 (5.0)	109 (5.6)	28 (3.6)	
AFP (>20 IU/mL)	325 (16.8)	224 (15.6)	101 (19.9)	0.026
HCV RNA (>600,000 IU/mL)	1,066 (48.1)	791 (48.0)	275 (48.5)	0.827
Liver biopsy	262 (9.5)	250 (12.8)	12 (1.5)	<0.001
FibroScan®	289 (11.7)	123 (7.4)	166 (20.5)	<0.001

Data are presented as mean±SD or number (%).
DAA, direct-acting antivirals; HBsAg, hepatitis B virus surface antigen; BMI, body mass index; HCC, hepatocellular carcinoma; GGT, gamma glutamyltransferase; ALT, alanine aminotransferase; UNL, upper normal limit; AFP, alpha fetoprotein; HCV, hepatitis C virus.
*Pre-DAA 2007–2014 vs post-DAA 2015–2017.

or fibrosis-4 score, also increased from the chronic hepatitis to the liver cirrhosis groups (Supplementary Table 2).

2. Laboratory and virologic characteristics and risk factors of Korean chronic HCV patients

About half of the patients (49.9%) showed an ALT level that was less than the upper normal limit of 40 IU/L, and only 5% showed a high ALT greater than five times the upper normal limit. The median HCV RNA level was 5.1×10^5 IU/mL, and HCV RNA levels exceeding 600,000 IU/mL, 2,000 IU/mL, and 1,000 IU/mL were found in 48.1%, 84.7% and 86.0% of the patients, respectively (Table 1). Therefore, a very low viral load of less than 1,000 IU/mL was observed in 14.0%, in whom HCV genotyping may be difficult. Moreover, the proportions of those for whom the HCV RNA level exceeded 600,000 IU/mL showed a significant difference among the three groups of patients (chronic hepatitis, 50.3%; liver cirrhosis, 45.1%; and HCC, 38.9%), suggesting a decreasing trend of the HCV RNA level according to disease progression (Supplementary Table 1).

Among the 2,078 patients who underwent an HCV genotype analysis (2,078/2,758, 75.3%), five genotypes were confirmed: genotype 1 (n=1,088, 52.4%), genotype 2 (n=964, 46.4%), genotype 3 (n=13, 0.6%), genotype 4 (n=3, 0.2%), and genotype 6 (n=10, 0.5%). As indicated, genotypes 1 and 2 accounted for 98.8%. The detailed subgenotype distribution is summarized in Table 2. The genotype 1b patients (47.8%) were significantly younger (55.5±12.6 years) than the genotype 2 patients (58.2±12.8 years, p<0.001), with a higher proportion of males (53.6% vs 44.6%, p<0.001), a higher proportion of decompensated cirrhosis (9.4% vs 5.2%, p=0.004), and a higher proportion of those with high HCV RNA levels exceeding 600,000 IU/mL (59.3% vs 43.4%, p<0.001). Moreover, the proportions of those who reported IVDU (14.0% vs 6.1%, p<0.001), needle stick injuries (16.0% vs 11.0%, p=0.026), and multiple sexual partners (≥4) (23.2% vs 14.9%, p<0.001) were higher in patients with genotype 1b than with genotype 2 (Supplementary Table 3).

Among the risk factors related to HCV infection, a history of blood transfusion before HCV screening was found in 14.3%, IVDU in 5.6%, needle stick injuries in 6.9%, tattoos in 37.4%, piercing in 33.5%, surgery in 56.9%, living with an HCV carrier in 3.2%, and currently on hemodialysis in 1.1%. Moreover, lifetime histories of dental procedures, endoscopy, and acupuncture were found in approximately 90% of the entire cohort. There were remarkable differences in risk factors between men and women. The proportions reporting IVDU experience, needle stick injuries, and having more than four sexual partners were significantly higher in men than in women, while the proportions who reported remote blood transfusions, tattooing, piercing and acupuncture were significantly higher in women than in men (Table 1).

3. Comparison of the clinical characteristics between pre- and post-DAA approval and comorbidities in HCV patients

The comparison of the clinical characteristics of the HCV patients between the pre- and post-DAA approval periods is summarized in Table 3. The mean age of the patients, the male proportion and the proportion of HCC patients increased from the pre-DAA era to post-DAA approval. Moreover, the proportion of patients with a normal range of the ALT level was higher in the post-DAA than in the pre-DAA period. Overall, liver biopsy was performed in 262 patients, and FibroScan® was carried out in 289, showing that the liver biopsy rate was reduced dramatically, whereas the rate of having undergone the FibroScan® increased significantly after DAA approval (Table 3).

Various extrahepatic cancers were found in 8.7% of the entire cohort of patients. The comorbidities of HBsAg positivity (3.3%), diabetes (18.6%), cardiovascular disease (25.7%), psychiatric (4.2%), and cerebrovascular diseases (1.8%) were found.

4. Treatment rate and clinical factors related to treatment in the pre- and post-DAA approval groups

The treatment patterns are shown in Fig. 3, in Table 4, and in Supplementary Table 4, in which the overall treatment rate is shown to be 53.8% (1,450/2,758). The antiviral regimen was based on interferon in 25.5%, and it was DAA therapy in 28.3%, consisting of 23.4% undergoing a treatment as naïve patients and 4.9% who had experienced interferon. The results of the comparison of the treatment patterns from the pre- and post-DAA periods are presented in Fig. 4. In the pre-DAA period, 34.8% received interferon-based therapy, whereas 11.5% (naïve) and 6.6% (interferon-experienced) of the cohort were treated with various types of DAA, mostly in a clinical trial set-

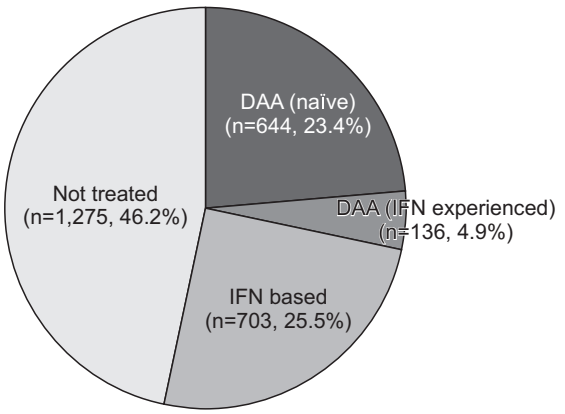

Fig. 3. Treatment patterns in the Korean hepatitis C virus cohort from 2007 to 2017. The antiviral regimen was based on interferon (IFN) for 25.5% and was based on direct-acting antivirals (DAA) for 28.3%, of whom 23.4% were IFN-naïve patients, and 4.9% had experience with IFN.

Table 4. Comparison of Clinical Characteristics According to Treatment in the Post-DAA Period

Variable	Post-DAA 2015–2017 (n=808)	Not treated (n=355)	Treated (n=453)	p-value
Age, yr	60.0±13.6	61.7±12.8	58.7±13.1	0.001
10–19	4 (0.5)	1 (0.3)	3 (0.7)	0.001
20–29	8 (1.0)	2 (0.6)	6 (1.4)	
30–39	26 (3.3)	10 (2.8)	16 (3.6)	
40–49	119 (15.0)	54 (15.4)	65 (14.6)	
50–59	237 (29.8)	82 (23.4)	155 (34.9)	
60–69	235 (29.6)	106 (30.2)	129 (29.1)	
≥70	166 (20.9)	96 (27.4)	70 (15.8)	
Male sex	435 (53.8)	190 (53.5)	245 (54.1)	0.873
Education				
Above high-school level	416 (52.1)	155 (43.9)	261 (58.5)	<0.001
Smoking (current or former)	374 (46.7)	170 (48.2)	204 (45.5)	0.460
Alcohol (current or former)	408 (50.6)	177 (49.9)	231 (51.1)	0.725
Diagnostic distribution				
Chronic hepatitis	559 (69.2)	222 (62.5)	337 (74.4)	<0.001
Liver cirrhosis	138 (17.1)	61 (17.2)	77 (17.0)	
Hepatocellular carcinoma	111 (13.7)	72 (20.3)	39 (8.6)	
HCV RNA, quantification				
>600,000 IU/mL	275 (48.5)	94 (42.4)	178 (52.7)	0.016
>2,000 IU/mL	485 (85.5)	172 (75.1)	313 (92.6)	<0.001
>1,000 IU/mL	494 (87.1)	176 (76.9)	318 (94.1)	<0.001
Treatment rate according to year of cohort enrollment				
Enrolled at 2015		110 (47.0)	124 (53.0)	0.459
Enrolled at 2016		130 (43.8)	167 (56.2)	
Enrolled at 2017		115 (41.5)	162 (58.5)	
Treatment rate according to the liver disease severity				
Chronic hepatitis	559 (69.2)	222 (62.5)	337 (74.4)	<0.001
Cirrhosis	138 (17.1)	61 (17.2)	77 (17.0)	
Hepatocellular carcinoma	111 (13.7)	72 (20.3)	39 (8.6)	
Behavior factors				
Intravenous drug use	45 (5.6)	21 (5.9)	24 (5.3)	0.704
Needle stick injury	30 (3.7)	8 (2.3)	22 (4.9)	0.052
Transfusion before 1995	77 (9.5)	30 (8.5)	47 (10.4)	0.355
Tattooing	286 (35.4)	118 (33.2)	168 (37.1)	0.256
Piercing	243 (30.1)	92 (25.9)	151 (33.3)	0.022
Acupuncture	634 (78.5)	257 (72.4)	377 (83.2)	<0.001
Living with HCV carrier	25 (3.3)	13 (3.9)	12 (2.8)	0.384
Hemodialysis	9 (1.1)	5 (1.4)	4 (0.9)	0.480
No. of sexual partner ≥4	145 (19.4)	57 (17.2)	88 (21.1)	0.176
Dental procedure	746 (92.3)	325 (91.5)	421 (92.9)	0.462
Endoscopy	704 (87.1)	310 (87.3)	394 (87.0)	0.883

Data are presented as mean±SD or number (%).
DAA, direct-acting antivirals; HCV, hepatitis C virus.

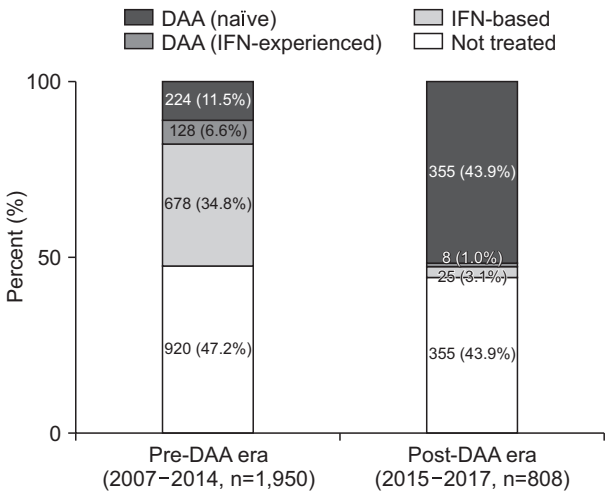

Fig. 4. Comparison of treatment patterns in the pre- and post-DAA approval periods in the Korean hepatitis C virus cohort. In the pre-DAA approval period, 34.8% received interferon (IFN)-based therapy. In the post-DAA approval period, only 3.1% of the patients underwent IFN-based therapy, while 44.9% received DAA therapy. DAA, direct-acting antivirals.

ting. However, in the post-DAA period, only 3.1% of patients underwent interferon-based therapy, while 44.9% received DAA therapy, which demonstrated that DAA therapy was rapidly replacing interferon-based therapy. However, even during the post-DAA period, 43.9% of patients remained untreated. Because patients were enrolled in 2015 to 2017, the follow-up period was less than 3 years, which may affect the low treatment rate. The treatment rates in the patients enrolled in 2015, 2016, and 2017 were 53.0%, 56.2%, and 58.5%, respectively.

To attempt to determine the cause of the nontreatment choices in the post-DAA period, the clinical characteristics were compared between "treated" and "non-treated" groups consisting of 808 patients who were enrolled in the post-DAA period (Table 4). The "non-treated" group showed a higher mean age, a lower educational level, and a higher proportion of HCC than the "treated" group. In addition, the "non-treated" group showed fewer patients with HCV RNA levels exceeding 600,000, 2,000, or 1,000 IU/mL than in the "treated" group, suggesting a higher proportion of low-titer carriers. However, there were no significant differences with regard to the risk factors related to HCV infection between the "treated" and "not treated" groups. Among 1,950 patients who were enrolled in the pre-DAA period, the comparison between the treated and non-treated groups showed features similar to those in the post-DAA period (Supplementary Table 4).

DISCUSSION

In this prospective cohort study, 2,758 Korean patients with chronic HCV infection showed a mean age of 57 years and a male-to-female ratio of 1.03. Approximately 90% of the patients were asymptomatic upon their diagnosis of HCV infection, and half of the patients' ALT levels were normal. Genotypes 1b and 2 accounted for more than 95% of all types, and viral loads of less than 1,000 IU/mL were observed in 14.0%. Histories of remote blood transfusion and IVDU were found in 14.3% and 5.6% of the cohort, respectively, indicating that the majority of these patients may have been infected in healthcare or cosmetics settings. The overall treatment rate of the entire cohort was 53.8%, showing a rapid transition from interferon-based to DAA therapies. Compared to the "treated" group, the "non-treated" group showed a higher mean age, a lower educational level, and a higher proportion of HCC. Fortunately, the proportion undergoing antiviral treatments increased since the advent of the DAA option.

Owing to effective prevention by HCV screening of blood transfusions by means of nucleic acid testing and improvements in healthcare quality levels, the incidence of HCV appears to be decreasing in South Korea. However, approximately 90% of the patients were asymptomatic upon the diagnosis of hepatitis C, and about half showed ALT levels within normal limits in this study. More than 90% of the Korean HCV cohort patients here were aged over 40 years, which is comparable to the nationwide anti-HCV prevalence in Korea.[11] Therefore, targeting the birth cohort showing high anti-HCV prevalence (i.e., population of 40 to 65 years of age) is a reasonable strategy for HCV control,[12] and this concept is supported by a recent study which showed that the one-time anti-HCV screening of the Korean population aged 40 to 65 would be highly cost-effective in Korea.[13]

The demographic characteristics of HCV patients differ greatly around the world depending on the region. The median/mean age of HCV patients was 48 years in Switzerland (2012 to 2015), 48.5 years in the United Kingdom (2012 to 2015), and 50.6 years in the United States according to claims data in 2014. Thus, all were younger than the Korean HCV cohort on average.[14-16] This difference may be related to the different risk factors of HCV infection, in this case the high prevalence of IVDU in the Western cohorts (>30%), in contrast to the Korean cohort (5.6%), as IVDU is more common in young males than in older or female populations.[17] Our results also showed that the risk factor profiles for HCV infection were significantly different between male and female patients. The proportions reporting IVDU and having more than three sexual partners were higher in male HCV patients, while those for transfusions, piercing, tattooing, acupuncture and endoscopy were higher in female patients. Male patients showed a younger mean age, a higher proportion of HCC, higher frequencies of alcohol intake and smoking, a higher frequency of abnormal ALT levels and a higher genotype 1 proportion than female patients. The proportion of HCC in the entire cohort was 11.5%, which appears to be higher compared to Western data[18,19] and which may be related to the older age of our cohort or a higher coinfection rate with HBV. Cardiovascular disease and cancer comorbidity rates

were higher in post-DAA approval than pre-DAA period, which seemed to be related to higher mean age of the patients enrolled in post-DAA approval period. Likewise, higher HBsAg positive rate in post-DAA approval was related to higher mean age of the patients, but the reason should be studied further.

We investigated the relationship between age and the degree of fibrosis according to a liver biopsy, finding that the proportion of biopsy-proven advanced fibrosis (F3, F4) increased significantly with an increase in age. Moreover, the proportions of advanced fibrosis in the Korean patients aged between 40 and 60 years (27%) and aged over 60 years (44%) were similar to those in European or other cohorts.[20,21]

Although a relationship between the HCV RNA titer and liver fibrosis has not yet been established, the median HCV RNA level was significantly higher in patients with chronic hepatitis than in patients with cirrhosis in this study.[22,23] While some studies have reported that high HCV RNA levels were correlated with advanced liver fibrosis,[24,25] another did not show a significant correlation between the viral level and fibrosis,[26] and further research is needed to determine whether a relationship exists between liver fibrosis and HCV RNA levels.

Interestingly, HCV RNA levels of less than 1,000 IU/mL were observed in 14% of the entire cohort, which may result in difficulty during genotyping testing. Because HCV viral titer is stable in chronic infection, the high proportion of low titer carrier may be related to the favorable genetic polymorphism of IL28B in Korean population, though we did not confirm. Compared to patients with HCV RNA levels greater than or equal to 1,000 IU/mL, the patients with HCV RNA levels of less than 1,000 IU/mL were younger and more likely to show a normal range of ALT levels, but the disease severity levels and genotypes did not differ (Supplementary Table 5). Ticehurst *et al*.[27] reported that high viral loads were associated with male sex, age exceeding 40 years, a higher body mass index and higher fibrosis and inflammation scores, findings which are in somewhat good agreement with the present results.

The major HCV genotypes in the Korean HCV cohort were genotypes 1b and 2, accounting for 95% of the total. These genotypes are easy to treat compared to genotype 3. Compared to genotype 2, genotype 1b patients are younger, more commonly male, and show higher decompensated cirrhosis and higher viral loads. However, the proportion of HCC did not differ between these two genotypes.[12] The common comorbidities found in HCV patients were cardiovascular disease and diabetes. The HBV coinfection rate was 3.3%, which appears to be similar to that of the general population of South Korea.[28]

There have been dramatic changes since the approval of the DAA therapy route in 2015, as that option is rapidly replacing interferon-based therapy. However, the overall treatment rate did not increase significantly after DAA approval. According to the HCV treatment cascade in the US, 50% of chronic hepatitis C patients are aware of their infection, the rate of hospital visits to identify HCV RNA is 27%, and only 16% of these patients receive a proper antiviral treatment (2003 to 2013; interferon-based treatment era),[16] showing a treatment rate of 59% among HCV viremic patients, similar to our result of 56% in the post-DAA era. However, the treatment rate in this study in 2017 was 58.5%, which is much higher than the results published by the World Health Organization, most likely because the subjects and their physicians in this study were highly motivated to undertake antiviral treatments at tertiary centers.[29]

In the DAA era, the "non-treated" group in this study showed a higher mean age, lower educational level, and higher proportion of HCC than the treated group in the post-DAA period, suggesting that awareness by the patients and socioeconomic factors such as the affordability of drugs affect the treatment rate. International practice guidelines recommend DAA therapy for HCC patients in a controlled state of HCC owing to the concern over the increased recurrence of HCC after DAA therapy.[30] The national insurance of Korea pays for DAA therapy only when HCC patients show the complete response state, which influences the low treatment rate in HCC patients in South Korea.

To improve the rate of HCV treatment, the one-time anti-HCV screening of the Korean population aged 40 to 65 by adding anti-HCV test to the National Health Examination Program[13] could be very cost-effective. Otherwise, action to increase the awareness of HCV infection and high cure rate of current DAA therapy among the general population and primary physicians is urgently needed. Though National Health Insurance partly reimburse, the cost of DAA is still not affordable to many patients, such as elderly or less educated patients as shown in this study. Therefore, efforts to reduce the drug cost are needed to raise treatment rate.

This study has several limitations. First, seven university hospitals participating in this study may not be representative of patients nationwide with chronic HCV infection in South Korea. Second, recall bias may have arisen when gathering the results of the questionnaires. There may also be sensitive personal data missing, such as IVDU or problems related to sexual patterns. Third, the data collected on the behavioral factors related to HCV infection are insufficient to determine whether these factors make any measurable contribution to overall HCV transmission rates. Fourth, there was no question on the reason of "not treated" in the questionnaire for "not treated patients," so that this could be included in the future study. Finally, the participating hospitals are the most active groups involved in antiviral treatments, implying that the true national treatment rate may be overestimated.

In conclusion, more than 90% of chronic hepatitis C patients were aged over 40 years and the major genotypes were 1b and 2 in Korea, where the IVDU rate is less than 6% among HCV patients. Approximately half of the patients underwent antiviral therapy even in the DAA era, demonstrating an unmet need for greater HCV elimination efforts.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This study was supported by a grant of the Chronic Infectious Disease Cohort Study (Korea HCV Cohort Study, 4800-4859-304) from the Korea Centers for Disease Control. This study was supported by a grant from a grant for the Chronic Infectious Disease Cohort Study (Korea HCV Cohort Study, 2017E5100100) from the Korea Centers for Disease Control and Prevention.

We are grateful to the devoted collaborators (Dawoon Jeong, Hye yean No, Ha yun Jung, Hye won Kim, Young soon Kim, Se min Na, Eun mi Yu, Hyoyoung Kang).

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