

Clinical Features and Outcomes of Patients With Genotype 3 Hepatitis C Virus Infection in Korea

A Retrospective Observational Study

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Abstract: Hepatitis C virus (HCV) genotype 3 infection is very rare in high-income Asia Pacific. The aim of our retrospective observational study was to evaluate the incidence, clinical features, and treatment outcomes of patients with a genotype 3 HCV infection in the Gyeongnam Province of Korea. Ninety-eight consecutive patients diagnosed with a genotype 3 HCV infection at Gyeongsang National University Hospital, between January 2005 and December 2014, were enrolled into the study. Relevant characteristics of the study group included: 80.6% men, mean age of 41.8 years, and including 69 patients with chronic hepatitis, 25 with liver cirrhosis, and 4 with hepatocellular carcinoma (HCC). Risk factors for HCV infection, sustained virologic response rate, development of HCC, and mortality in patients with genotype 3 were retrospectively analyzed.

Among all patients diagnosed with a HCV infection during the study period, the prevalence of genotype 3 was 7.3%. The incidence of genotype 3 was higher in young patients with a risk factor of IVDU (54.0%) and tattooing (62.3%). Among 45 treatment-naïve genotype 3 patients, sustained virologic response was achieved with a combination of pegylated-interferon alpha and ribavirin in 75.6%. The cumulative 5-year incidence of HCC was 13.6%, and 8.9% for overall mortality. Liver cirrhosis at enrollment was an independent risk factor for HCC development.

This is the first study to elucidate the clinical features and outcomes among the patients with HCV genotype 3 infection in Korea. Further prospective studies are needed to investigate transmission routes and outcomes for HCV genotype 3 infections.

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Abbreviations: ALT = serum alanine aminotransferase, anti-HBs = anti-hepatitis B virus surface antibodies, CI = confidence interval, CT = computed tomography, DAAs = direct acting agents, HBsAg = hepatitis B virus surface antigens, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HR = hazard ratio, IVDU = injecting drug users, SVR = sustained virologic response.

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of liver cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease. The natural course of HCV infection is variable, with the progression of liver cirrhosis extending over 2 or 3 decades in 20% to 30% of patients with an HCV infection. Once cirrhosis evolves, HCC develops in 1% to 4% of patients per year.^{1,2} The progression of chronic hepatitis C is not linear, with several factors being associated with a rapid progression. These factors include the genotype of the viral infection, viral load, age at the time of infection, body mass index, alcohol consumption, and coinfection of hepatitis B virus (HBV) or human immunodeficiency virus (HIV).³ HCV genotype is specifically important in predicting a patient's response to antiviral therapy. Therefore, genotype determination is the first step in the diagnosis and treatment of HCV infection.⁴ Moreover, the genotype may be an important factor contributing to the severity and aggressiveness of the liver disease.^{5,6}

The distribution of HCV genotypes differs in various countries. Globally, genotype 1 is the most prevalent,⁷ followed by genotype 3 which accounts for an estimated 30% of cases of HCV infection worldwide. Approximately three-quarters of all infections with the genotype 3 virus strain occur in South Asian countries, as for example in India and Pakistan, indicating a geographic distribution of HCV genotypes. Transmission of specific HCV genotypes is further influenced by behavioral risk factors, with genotype 3a being particularly prevalent in injection drug users (IVDU) in Western Europe and the United States.⁸

As treatment for HCV has evolved, infection with the genotype 3 virus has become one of the most difficult forms of HCV to treat,⁹ with a more rapid progression to fibrosis and cirrhosis compared with HCV infections by other genotypes.^{10–12} HCV genotype 3 infection is associated with a higher prevalence of severe steatosis and increased risk for HCC and mortality from all causes.^{10,13,14}

Previous studies evaluating the outcomes of genotype 3 HCV infections have included very few patients specifically

infected with the genotype 3 strain of the virus.^{14,15} Therefore, there is a need to better understand the effects of genotype 3 on the natural progression of HCV infection, as well as to clarify routes of transmission of the genotype 3 virus and its response to treatment. This information is of interest worldwide, and specifically in Korea where HCV infection is most commonly associated with genotypes 1 and 2,¹⁶ with no available studies regarding the clinical features and outcomes of patients with genotype 3. Therefore, the aims of our study were to investigate the risk factors related to HCV genotype 3 infection and to a sustained virologic response (SVR), as well as to evaluate the incidence rate of HCC and overall mortality in patients infected with the genotype 3 virus in Korea.

METHODS

Patients

We retrospectively identified and enrolled a total of 1335 consecutive patients, aged >20 years, who received treatment for chronic HCV infection, with a detectable HCV genotype, at the Gyeongsang National University Hospital, between January 2005 and December 2014. Among these patients with HCV infection, a genotype 3 HCV was confirmed in 98 (7.3%) patients. The following data were collected from the electronic medical records of these 98, genotype 3-infected patients with HCV. Results of laboratory tests included anti-HCV, serum HCV-RNA levels, hepatitis B virus surface antigens (HBsAg), anti-hepatitis B virus surface antibodies (anti-HBs), HIV-antibodies, serum albumin levels, serum alanine aminotransferase (ALT) levels, serum total bilirubin levels, and serum platelet counts. Comorbidities, including liver cirrhosis, chronic kidney disease, diabetes mellitus, HCC, and fatty liver disease, were recorded. The medical and personal history was carefully reviewed to identify exposure to various risk factors, such as a previous history of blood transfusion or surgery; alcohol intake; and high risk behavior, including tattoos, piercings, IVDU, and acupuncture. The present study was approved by the Institutional Review Board of the Gyeongsang National University Hospital.

Follow-Up and Definition of Clinical Outcomes

All patients were monitored for laboratory test and imaging examinations, such as ultrasonography and computed tomography (CT), every 3 to 12 months. Antiviral therapy, using pegylated-interferon alpha and ribavirin, was administered according to individual treating physician's decision, as direct acting agents (DAAs) were not available in Korea during the study period. Time to event was calculated from the date of identification and inclusion in the study group to the date of occurrence of HCC, death, last observation, or June 30, 2015. To calculate cumulative incidences of HCC and overall mortality rates in patients with a genotype 3 infection, we excluded patients with less than 6 months of follow-up or patients with

HCC diagnosed within 6 months of enrollment in the study. The diagnosis of HCC was based on histological examinations or typical radiographic findings consisting of hypervascularity in the arterial phase, with washout in the portal or delayed phases, of hepatic nodules on contrast-enhanced CT or magnetic resonance imaging.¹⁷ Fatty liver disease was diagnosed by radiological imaging, based on findings of hepatomegaly, diffuse increase in echogenicity of the liver parenchyma, and vascular blunting identified on ultrasound or CT images. Heavy alcohol drinking was defined as >40 g/day.

Statistical Analysis

Continuous variables were expressed as a mean \pm standard deviation. Between-group differences were evaluated using the Mann–Whitney *U* test for quantitative data and χ^2 or Fisher exact tests for qualitative data. The cumulative incidence rate of HCC and overall mortality were calculated using the Kaplan–Meier method and compared using the log-rank test. To identify factors associated with HCC and mortality, univariate and multivariate analyses were performed using the Cox proportional hazard model. The risk was expressed as a hazard ratio (HR) and its associated 95% confidence interval (CI). All analyses were 2-sided and a *P* value <0.05 considered to be statistically significant. Statistical analyses were performed using PASW software (Version 18, SPSS Inc, Chicago, IL).

RESULTS

Patients' Characteristics

Over the study period, a total of 1335 patients tested positive for HCV infection in our hospital. Among these, a HCV genotype 1 was identified in 556 patients (41.7%), a genotype 2 in 678 (50.8%) patients, and a genotype 3 in 98 (7.3%) patients, with 3 (0.2%) patients identified with other genotypes of HCV infection (Table 1). Patients with genotype 3 infections were younger (mean age, 41.8 \pm 10.5 years) compared with patients with genotype 2 (57.2 \pm 13.4 years, *P* < 0.001) and genotype 1 (56.2 \pm 12.7 years, *P* < 0.001) infection.

The baseline characteristics of the 98 patients with a HCV genotype 3 infection are summarized in Table 2. Among this patient subgroup, 69 (70.4%) were diagnosed with chronic hepatitis, 25 (25.5%) with liver cirrhosis, and 4 (4.1%) with HCC. Genotype 3a was present in 95 (96.9%) of patients; in the remaining 3 (3.1%) of patients, the subgenotype could not be typed. At the time of identification for the study, 31 (31.6%) of patients with a genotype 3 infection had fatty liver disease. The median follow-up duration of patients was 48.2 months.

Behavioral Risk Factors in Genotype 3 Infection

Behavioral risk factors for HCV genotype 3 infections were obtained by a review of patients' medical charts. The

TABLE 1. Comparison of Mean Age and Sex, According to Hepatitis C Virus Genotypes (n = 1335)

Variable	Genotype 1	Genotype 2	Genotype 3	Others
Numbers	556 (41.7%)	678 (50.8%)	98 (7.3%)	3 (0.2%)
Age at enrollment	56.2 \pm 12.7*	57.2 \pm 13.4*	41.8 \pm 10.5	49.0 \pm 6.6
Male	460 (82.7%)	522 (77.0%)	79 (80.6%)	2 (66.7%)

Data are presented as the mean \pm standard deviation for continuous data and percentages for categorical data.

**P* value <0.001 compared with genotype 3 using Mann–Whitney test.

TABLE 2. Baseline Characteristics of the 98 Patients With Hepatitis C Virus Genotype 3

Variable	n = 98
Diagnosis at enrolment	
Chronic hepatitis	69 (70.4%)
Liver cirrhosis	25 (25.5%)
Hepatocellular carcinoma	4 (4.1%)
Fatty liver at enrollment (n = 95)	31 (31.6%)
Alcohol >40 g/d	53 (54.6%)
HBsAg	4 (4.1%)
Diabetes	24 (24.5%)
HIV	0 (0.0%)
Subgenotype	
3	3 (3.1%)
3a	95 (96.9%)
HCV RNA > 600,000 IU/mL at enrollment	56 (57.1%)
Type of risk factor*	
IVDU (n = 63)	34 (54.0%)
Tattoo (n = 69)	43 (62.3%)
Surgery (n = 83)	42 (50.6%)
Transfusion before 1992 (n = 73)	14 (19.2%)
Acupuncture (n = 64)	20 (31.3%)
Body piercing (n = 68)	12 (17.6%)
Imprisonment (n = 75)	5 (6.7%)
Antiviral treatment either before or after enrollment	56 (57.1%)
Follow-up period, mo	48.2 ± 53.1

Data are presented as the mean ± standard deviation for continuous data and percentages for categorical data.

HBsAg = hepatitis B surface antigen; HIV = human immune deficiency virus; IVDU = intravenous drug use.

*Data were missing in some patients.

possible behavioral risk factors related to HCV infection were as follows: IVDU (34/63, 54.0%), tattoo (43/69, 62.3%), surgery (42/83, 50.6%), transfusion before 1992 (14/73, 19.2%), acupuncture (20/64, 31.3%), body piercing (12/68, 17.6%), and imprisonment (5/75, 6.7%).

Antiviral Therapy and Response to Treatment

The study group was comprised of 98 patients with a genotype 3 infection. Of these 98 patients, 87 had not received antiviral treatment prior to enrollment into the study (treatment naïve group), while the remaining 11 patients had received antiviral treatment prior to enrollment.

Of the 98 patients forming our study group, 56 (57.1%) received antiviral therapy (11 before enrollment and 45 after enrollment), with the remaining 42 (42.9%) not receiving treatment. The most common reasons for nontreatment were: nonadherence with follow-up (45.3%); decompensated cirrhosis or HCC (26.2%); contraindication to interferon-based therapy, such as pregnancy, severe depression, and significant neuropsychiatric syndrome (21.4%); and patient refusal (7.1%).

From the treatment naïve group, 45 of the 87 patients received antiviral treatment using pegylated-interferon alpha and ribavirin. Of this group of 45 patients, 39 (86.7%) completed the antiviral therapy, with 34 achieving SVR (Figure 1). Among the 11 patients with a prior history of antiviral treatment, 2 had achieved SVR.

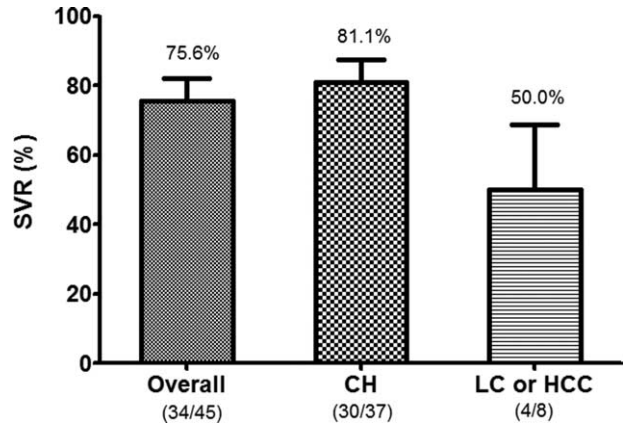


FIGURE 1. Sustained virologic response rate in treatment-naïve patients with genotype 3 infection.

It is interesting to note that among the treatment-naïve group, 37 patients had a clinical diagnosis of chronic hepatitis, 7 of liver cirrhosis, and 1 of HCC. The achievement rate of SVR was 81.1% in patients with chronic hepatitis and 50.0% in patients with liver cirrhosis or HCC.

Incidence of Hepatocellular Carcinoma and Mortality

We assessed the incidence of HCC development in patients who did not have a diagnosis of HCC at the time of enrollment. To calculate the true incidence of new HCC cases, patients with less than 6 months of follow-up or patients diagnosed with HCC within 6 months of enrollment were excluded. Therefore, the incidence rate for HCC and overall mortality from all causes in patients with a genotype 3 infection was calculated for 78 patients, 59 patients with chronic hepatitis, and 19 patients with liver cirrhosis. During a mean follow-up of 59.6 months, 9 (11.5%) patients were diagnosed with new HCC. The cumulative incidence of HCC at 3 and 5 years was 10.4% and 13.6%, respectively (Figure 2A). There was a significant difference in the development of HCC between patients with and without SVR (Figure 2B). Only one patient who achieved SVR developed HCC 12 months after completion of antiviral treatment. At the time of HCC diagnosis, this patient was evaluated to have Child-Pugh class A cirrhosis and underwent surgical liver resection at age 41. However, there was no significant difference in the development of HCC between patients with and without fatty liver at enrollment using the log-rank test ($P=0.052$).

Over the study period, 5 patients died. The cumulative incidence of overall mortality at 3 and 5 years was 5.5% and 8.9%, respectively (Figure 3A). There was significant difference in overall mortality between patients with and without SVR (Figure 3B). No death occurred among patients who achieved SVR during the follow-up period.

Predictive Factors Associated With Hepatocellular Carcinoma Development

On univariate analysis, age >40 years, cirrhosis at enrollment, alcohol consumption >40 g/day, achievement of SVR, and platelet counts were significant factors associated with the development of HCC (Table 3). On multivariate analysis, liver cirrhosis at enrollment was the only independent factor

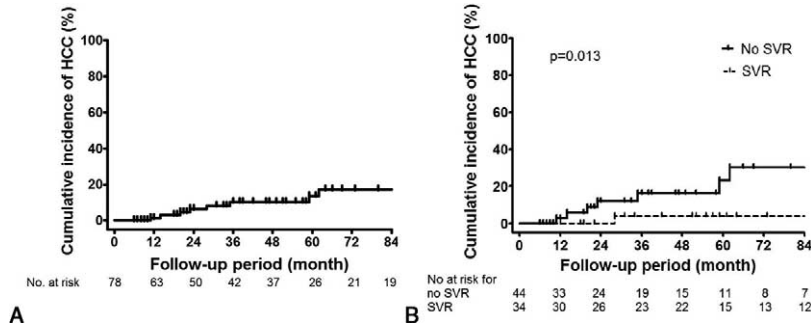


FIGURE 2. The cumulative incidence of hepatocellular carcinoma in patients with genotype 3 infection. A, The cumulative incidence of hepatocellular carcinoma at 3 and 5 years was 10.4% and 13.6%, respectively. B, Significant difference in the development of hepatocellular carcinoma between patients with and without sustained virologic response ($P=0.013$). SVR=sustained virologic response.

associated with the development of HCC (HR = 33.834, 95% CI = 2.088–548.269, $P=0.013$).

DISCUSSION

In our single center, retrospective, observational study of patients with HCV infection in Korea, we identified a prevalence of genotype 3 infection of 7.3%. Individuals at risk for genotype 3 infection were young, with a history of IVDU and tattooing. In our group of individuals with a genotype 3 infection, 81.1% had chronic hepatitis and 50.0% cirrhosis or HCC. Among this group, an SVR rate of 75.6% was achieved with the use of a combination of pegylated-interferon alpha and ribavirin. The cumulative incidence of HCC in patients with a genotype 3 HCV was 13.6% at 5 years, with an overall mortality rate of 8.9%. Liver cirrhosis at the time of inclusion into the study was an independent risk factor for HCC development.

The genotype distribution of HCV differs according to geographic regions and routes of transmission. In high income Asian Pacific countries, as for example Korea and Japan, genotype 1 and 2 account for the majority of HCV infections, with a low prevalence of genotypes 3, 4, 5, and 6.⁷ Several studies have in fact estimated the prevalence of genotype 3 infection in Korea to be 0% to 1.7%.^{16,18–21} The prevalence rate of IVDU in Korea has also been estimated to be low, at 0% to 6.4%, with a 12.3% to 36% rate for tattooing.^{16,21–23} We

performed our study in the Gyeongnam Province, located on the southeast coast of Korea. Interestingly, the prevalence of genotype 3 infection in this region was 7.3%, with a prevalence rate of IVDU of 54.0% and of tattooing of 62.3%. In a previous study, the prevalence of overall HCV infection in the Gyeongnam Province was more than twice that of the national average.²⁴ However, our specific findings for patients with a genotype 3 infection agree with previous studies having identified an association between genotype 3a HCV infection and IVDU and tattooing,^{25,26} with a reported HCV infection rate of 48.4% among IVDU users.²⁷ Therefore, our high prevalence of genotype 3 indicates that individuals from the coastal region of Korea share common behavioral risk factors, such as IVDU and tattooing, as well as having more frequent contact with foreigners than in other regions of Korea, which may increase their risk for HCV infection.

Traditionally, genotypes 2 and 3 HCV infections were classified as being “easier-to-treat” than other HCV genotypes. However, with advancement in HCV treatment, genotype 3 has become the most difficult-to-treat HCV genotype.⁹ The global rate of SVR among patients infected with genotype 3 HCV and treated with pegylated-interferon alpha and ribavirin has been estimated to be 65% to 70%.^{9,28,29} To the best of our knowledge, epidemiological studies on the rate of SVR for patients treated with pegylated-interferon alpha and ribavirin for a genotype 3 infection in high-income Asian Pacific countries have not been

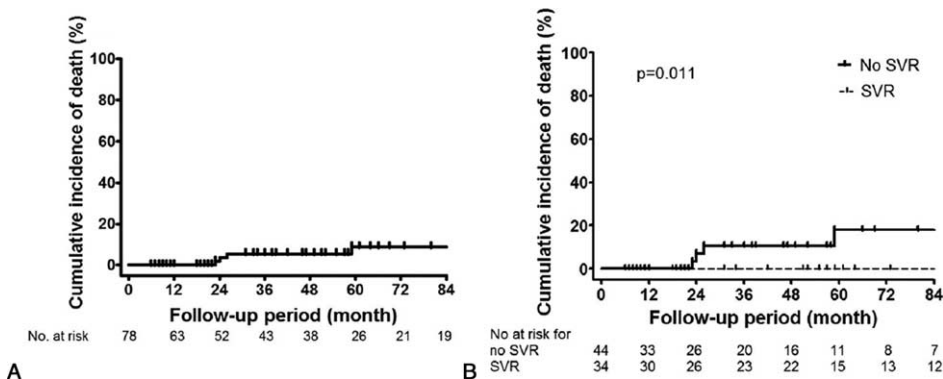


FIGURE 3. The cumulative incidence of overall mortality in patients with genotype 3 infection. A, The cumulative incidence of overall mortality at 3 and 5 years was 5.5% and 8.9%, respectively. B, There was a significant difference in overall mortality between the patients with and without sustained virologic response ($P=0.011$). SVR = sustained virologic response.

TABLE 3. Predictors for Development of Hepatocellular Carcinoma in Patients With Hepatitis C Virus Genotype 3 (n = 78)

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P Value	HR	95% CI	P Value
Male	27.304	0.016–45402.200	0.382			
Age >40 y	5.234	1.082–25.324	0.040	2.697	0.436–16.683	0.286
Cirrhosis at enrollment	54.32	6.292–470.473	<0.001	33.834	2.088–548.269	0.013
Fatty liver	0.027	0.000–10.437	0.236			
Diabetes	0.94	0.195–4.536	0.939			
Alcohol intake >40 g/d	9.946	1.238–79.915	0.031	8.556	0.693–105.623	0.094
IVDU	1.783	0.324–9.798	0.506			
Tattoo	2.967	0.363–24.247	0.310			
SVR	0.111	0.014–0.892	0.039	0.848	0.063–11.445	0.901
HCV RNA >600,000 IU/mL	1.77	0.367–8.546	0.477			
Albumin, IU/L	0.867	0.604–1.245	0.439			
AST, IU/L	1.002	0.997–1.007	0.450			
Platelet count (×10 ⁹ /L)	0.988	0.980–0.997	0.009	1.000	1.000–1.000	0.872
Total bilirubin, mg/dL	1.187	0.904–1.599	0.218			

AST = aspartate aminotransferase; CI = 95% confidence interval; HCV = hepatitis C virus; HR = hazard ratio; IVDU = intravenous drug use; SVR = sustained virologic response.

conducted. In our single-center study in 1 affluent region of Korea, the overall rate of SVR was 75.6% in treatment-naïve patients, which is comparable to previously reported SVR rates.^{28,29} In the 37 patients with chronic hepatitis, SVR was achieved in 30 (81.1%) patients, while in the 8 patients with cirrhosis or HCC, SVR was achieved in 4 (50.0%). In our study, 11 patients had received antiviral treatments prior to enrollment into the study. Among these patients, 4 were retreated with pegylated-interferon and ribavirins, with SVR achieved in 2 patients. We found that the combination of pegylated-interferon and ribavirin regimens was less effective in treatment-experienced patients (2/4, 50%) and in treatment-naïve patients with cirrhosis or HCC (2/4, 50%). Therefore, new DAA-based regimens should be used in these select populations in high-income locations of Pacific Asia.

In a retrospective study of 353 patients with HCV-related cirrhosis, the HCC incidence in patients with a genotype 3 infection was significantly higher than for other HCV genotypes, with 44% of patients with a genotype 3 infection and cirrhosis developing HCC and a 5-year occurrence rate of HCC of 34%.¹⁰ In a large multicenter retrospective study, genotype 3 infection was associated with a higher risk for HCC (HR of 2.08 compared with non-3 genotype) and mortality from all-causes (HR of 2.68 compared with non-3 genotype).¹⁴ In a retrospective cohort study of ~110,000 U.S. Veterans with HCV infection, genotype 3 was associated with a significantly higher risk of developing cirrhosis and HCC compared with genotype 1 infection.¹¹ In our study, the 5-year occurrence rate of HCC in patients with a genotype 3 infection was 13.6%, with a 5-year overall mortality rate of 8.9%. Identified risk factor for the development of HCC included older age, cirrhosis, alcohol consumption >40 g/day, achievement of SVR, and low platelet counts. However, on multivariate analysis, only liver cirrhosis at inclusion into the study was identified as an independent risk factor for the development of HCC in patients with a genotype 3 infection. This result of our multivariate analysis might be related to an insufficient sample size (n = 78), and larger, multicenter studies are needed to confirm risk factors associated with the development of HCC in patients with a genotype 3

HCV infection. The mechanism of HCC development in individuals with a genotype 3 infection is currently unknown. However, there is evidence for oxidative stress, lipid peroxidation, and pathways involved in steatogenesis, such as SREBP or FAS activation, contributing to hepatocarcinogenesis.^{30–32}

There are several limitations in our study, which need to be considered in the interpretation of results. Foremost, this is a retrospective, single-center study that limited comprehensive assessment of potential behavioral risk factors, duration of infection, actual amount of alcohol consumption, and response to antiviral treatment. In addition, our center is a tertiary referral center in the Gyeongnam Province, located on the southeast coast of Korea. Therefore, selection and referral bias might exist and our findings, such as the prevalence of HCV genotypes and potential risk factors for genotype 3 infection (ie, IVDU and tattoos), may not accurately represent the overall epidemiology of HCV in Korea. As an example, IVDU is not common in Korea. Our sample size of patients with a genotype 3 infection was relatively small compared with other reports from South Asian studies as genotype 3 infection tends to be low in high-income regions of Pacific Asia.

In conclusion, the prevalence of genotype 3 seems to be high in the Gyeongnam Province of Korea, especially in young individuals exposed to IVDU and tattooing, compared with those in other high-income Asian Pacific countries. The overall SVR rate was 75.6% in treatment-naïve patients, which is similar to previously reported rates in South Asia and Western countries. The cumulative incidence of HCC at 5 years was 13.6%, and liver cirrhosis at enrollment into the study was an independent risk factor for HCC development. Further prospective studies are warranted to comprehensively understand the transmission routes and clinical features of genotype 3 infections in regions of low endemicity for genotype 3 HCV infections.

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