pISSN 2287-2728
eISSN 2287-285X

CMH Original Article

http://dx.doi.org/10.3350/cmh.2012.18.2.219
Clinical and Molecular Hepatology 2012;18:219-224

Hepatitis C virus (HCV) genotypes and the influence of HCV subtype 1b on the progression of chronic hepatitis C in Korea: a single center experience

Eun Ju Cho, Su Hyeon Jeong, Byung Hoon Han, Sang Uk Lee, Byung Chul Yun, and Eun Taek Park

Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea

Background/Aims: There is some controversy regarding whether or not hepatitis C virus (HCV) subtype 1b is more influential than non-1b subtypes on the progression of chronic hepatitis (CH) C to liver cirrhosis (LC) and hepatocellular carcinoma (HCC).

Methods: We retrospectively analyzed 823 patients with chronic HCV infection, including 443 CH patients, 264 LC patients, and 116 HCC patients, who were HCV RNA positive and HBsAg negative. These patients had not received any prior treatment with either interferon alone or a combination of interferon and ribavirin.

Results: HCV subtypes 1b (51.6%) and 2a/2c (39.5%) were the two most common genotypes. The proportions of genotypes 2 (2a/2c, 2b, and 2) and 3 were 45.8% and 1.1%, respectively. One case of genotype 4 was found. HCV subtype 1b (47.3%) was less common than the non-1b subtypes (52.7%) in non-LC patients, but its proportion (56.9%) was higher than that of non-1b subtypes (43.1%) in LC patients (P=0.006). The proportions of patients with HCV subtype 1b did not differ significantly between the LC (55.3%) and HCC (60.3%) groups. Older age, male gender, and the relative progression of liver damage (non-LC vs. compensated LC vs. decompensated LC) were significant risk factors for HCC, with odds ratios of 1.081 (95% confidence interval [CI], 1.056-1.106), 5.749 (95% CI, 3.329-9.930), and 2.895 (95% CI, 2.183-3.840), respectively. HCV subtype 1b was not a significant risk factor for HCC (odds ratio, 1.423; 95% CI, 0.895-2.262).

Conclusions: HCV subtypes 1b and 2a/2c were the two most common HCV genotypes. HCV subtype 1b seemed to be more influential than non-1b subtypes on the progression of CH to LC, but not on the development of HCC from LC. **(Clin Mol Hepatol 2012;18:219-224)**

Keywords: Genotype; Hepatitis C; Hepatocellular carcinoma; Liver cirrhosis

INTRODUCTION

Among patients with advanced liver disease including liver cirrhosis (LC) and hepatocellular carcinoma (HCC), 11-17% are ascribed to hepatitis C virus (HCV) infection in Korea.[1,2] In clinical practice, HCV genotype can be determined by reverse hybridization analysis by using genotype-specific probes representing type-specific sequence patterns located in the 5′ non-coding and core-coding region.[3]

The HCV species have been classified into six genotypes (1 to

Abbreviations:

CH, chronic hepatitis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LC, liver cirrhosis

Corresponding author : Byung Hoon Han
Department of Internal Medicine, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 602-702, Korea
Tel. +82-51-990-6213, Fax. +82-51-248-5686
E-mail; bhhankosin@hanmail.net

Received : March 5, 2012
Revised : April 18, 2012
Accepted : April 24, 2012

6), and encompassing 18 subtypes (1a, 1b, 2a to 2c, 3a to 3c, 4a to 4h, 5a, and 6a).[3] The genotypes of HCV show a distinct geographical distribution. Genotypes 1, 2, and 3 are globally distributed.[4] Genotype 4 is the predominant genotype of the Middle East and Africa.[5] Types 5 and 6 are largely confined to South Africa and South East Asia, respectively.[6,7] HCV genotype 3 is particularly prevalent in intravenous drug abusers in Europe and the United States.[7] In Korea, genotypes 1 and 2 account for more than 99% of HCV species, genotype 3 seems to be found uncommonly (<1%),[8] and genotypes 4 and 5 have never been reported in the literature till date.

The genotype of the HCV strains appears to be an important determinant of the severity and aggressiveness of liver infection[9-14] as well as patient response to antiviral therapy.[9,15] HCV subtype 1b is known to be more closely associated with HCV-related LC[9,10] and HCC[10-14] than non-1b subtypes. HCV genotypes 2 and 3 show more than two times higher sustained virological response rates to conventional interferon-α therapy than genotype 1.[15] In contrast, there is still a possibility that the severity of liver disease due to chronic HCV infection is not varied depending on genotypes in untreated individuals.[16-20] We analyzed patients with HCV induced chronic liver disease to determine precisely the frequency of each HCV genotype and evaluate the influence of subtype 1b on the progression of chronic hepatitis (CH) to LC and HCC in Korea.

PATIENTS AND METHODS

Patients

We retrospectively analyzed 823 patients with positive for serum HCV-RNA by real-time polymerase chain reaction, who were consecutively admitted to the Liver Unit of Kosin University Hospital in Busan, Korea, between January 2004 and August 2011. All patients were serum HBsAg negative and had not received any prior treatment with interferon or interferon/ribavirin combination. This study population consisted of 443 patients with CH, 264 patients with LC, and 116 patients with HCC. The mean age of 823 patients was 55.5±10.9 years. Four hundred forty four subjects (53.9%) were male and 379 (46.1%) were female (Table 1).

The diagnosis of LC was made on laboratory and clinical basis: Child-Pugh Score ≥5, characteristic ultrasonographic findings such as a nodular liver surface, decreased right lobe-caudate lobe ratio, and indirect evidence of portal hypertension.[21,22] Patients who had Child-Pugh score more than 7 at base line with forementioned findings[21,22] of LC were considered to have decompensated LC.

Table 1. Clinical characteristics of patients with chronic HCV infection

Variables	Characteristics (n=823)
Age (yr)	55.5±10.9
M/F	444/379
HCV genotype	
1	435 (52.9)
1	1 (0.1)
1a	9 (1.1)
1b	424 (51.6)
a/b	1 (0.1)
2	377 (45.8)
2	20 (2.4)
2b	32 (3.9)
2a/2c	325 (39.5)
3	9 (1.1)
3	8 (1.0)
3a	1 (0.1)
4	1 (0.1)
1+2	1 (0.1)
Liver Disease	
CH	443 (53.8)
LC	264 (32.1)
Compensated LC	152 (18.5)
Decompensated LC	112 (13.6)
HCC	116 (14.1)
CH	19 (2.3)
Compensated LC	34 (4.1)
Decompensated LC	63 (7.7)

Values are presented as mean±SD or number (%).
HCV, hepatitis C virus; CH, chronic hepatitis; LC, liver cirrhosis; HCC, hepatocellular carcinoma.

We regarded the following masses as hepatocellular carcinoma: the mass showing arterial enhancement in the hepatic arterial phase and washout during portal phase on liver 3-phase CT, or the other mass with high serum alpha-fetoprotein (≥200 ng/mL).[23,24] We did needle biopsy on mass with non-characteristic hemodynamics on liver 3-phase CT and low serum alpha-fetoprotein (<200 ng/mL).

HCV RNA measurement and genotyping

HCV RNA was measured using real-time polymerase chain reaction assay (CE-marked COBAS® Ampliprep/COBAS® Taqman® HCV

http://dx.doi.org/10.3350/cmh.2012.18.2.219

test, Roche Diagnostics, Basel, Switzerland) with a lower detection limit of 10 IU/mL. HCV genotypes were determined by a line-probe assay (INNO-LiPA HCV II, Innogenetics, Ghent, Belgium) in serum samples of all patients with HCV RNA positive.[3] Hybridization of 5′ non-coding and core-coding region amplification products with genotype and subtype specific probes are capable of discriminating among HCV subtypes 1a, 1b, 2a to 2c, 3a to 3c, 4a to 4h, 5a, and 6a.[3]

Statistical analysis

We analyzed patient's continuous data (age) by using independent-samples *t* test and one way ANOVA, and categorical data (the ratios of males to females, LC to non-LC, HCV subtype 1b to non-1b subtypes, and HCC to non-HCC) by using the chi-square test. To clarify the factors associated with the development of HCC, we estimated the influences of the presumptive independent variables such as age, male sexuality, HCV subtype 1b, and the progression of liver damage (non-LC, compensated LC, and decompensated LC) by using multiple logistic regression analysis. The results were evaluated with a significant level of $P<0.05$.

RESULTS

The distribution of HCV genotypes

This study showed that HCV subtypes 1b (51.6%) and 2a/2c (39.5%) were the two most common HCV genotypes, followed by 2b (3.9%), 2 (2.4%), 1a (1.1%), 1 (0.1%), 1a/1b (0.1%), 3 (1.0%), 3a (0.1%), 4 (0.1%), and 1+2 (0.1%). The proportion of genotype 2 (2a/2c, 2b, and 2) was 45.8% (Table 1).

The clinical differences between the groups of patients with HCV subtype 1b and non-1b without considering the presence of HCC

When we divided the patients into two groups of patients with non-LC and LC without considering the presence of HCC, HCV subtype 1b (47.3%) was less common than non-1b subtypes (52.7%) in the group of patients with non-LC, but its proportion (56.9%) was higher than that of non-1b subtypes (43.1%) in the group of patients with LC. Difference between these two groups was significant ($P=0.006$). The mean age and the ratio of males to females in the group of patients with HCV subtype 1b (55.3±10.7 years and 239/185) were not different significantly from those in the group of patients with non-1b subtypes (55.7±10.9 years and 205/194) (Table 2), Though the difference was not statistically significant, the mean age of the non-LC (52.7±10.5 years vs. 53.0±10.3 years, $P=0.70$) or LC (58.1±10.4 years vs. 59.7±10.8 years, $P=0.14$) group of patients with subtype 1b was lower than that of the non-LC or LC group of patients with non-1b subtypes (Table 3).

The clinical differences between the groups of patients with CH, LC, and HCC

The age differences between the groups of patients with CH (52.3±9.9 years), LC (57.6±10.6 years), and HCC (62.6±10.0 years) were statistically significant ($P<0.001$). The ratio of males to females were significantly ($P<0.001$) higher in the group of patients with HCC (92/24) than in the group of patients with CH (213/230) or LC (139/125). The proportion of HCV subtype 1b was significantly higher ($P=0.012$) in the group of patients with LC (55.3%) or HCC (60.3%) than in the group of patients with CH (47.0%),

Table 2. Clinical differences between the groups of patients with HCV subtypes 1b and non-1b, irrespective of the presence of HCC

HCV subtype	1b	non-1b	Total	*P*-value
Number (%)	424 (51.5)	399 (48.5)	823 (100.0)	
Age (yr, mean±SD)	55.3±10.7	55.7±10.9	55.5±10.8	0.501*
M/F	239/185	205/194	444/379	0.129†
Liver damage				0.006†
Non-LC (%)	218 (47.3)	243 (52.7)	461 (100.0)	
LC (%)	206 (56.9)	156 (43.1)	362 (100.0)	
Compensated (%)	105 (56.1)	82 (43.9)	187 (100.0)	
Decompensated (%)	101 (57.7)	74 (42.3)	175 (100.0)	

*Independent-samples *t*-test and †Chi-square test.
HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LC, liver cirrhosis.

 http://dx.doi.org/10.3350/cmh.2012.18.2.219

Table 3. Age differences between non-LC and LC patients among those with HCV subtype 1b and non-1b

	Subtype 1b	Non-1b subtypes	*P*-value*
Non-LC (yr)	52.7±10.5	53.0±10.3	0.70
LC (yr)	58.1±10.4	59.7±10.8	0.14

Values are presented as mean±SD.
*Independent-samples *t*-test.
HCV, hepatitis C virus; LC, Non-LC, non-liver cirrhosis; LC, liver cirrhosis.

Table 4. Clinical differences between the CH, LC, and HCC patients with chronic HCV infection

	CH	LC	HCC	*P*-value
Total (n)	443	264	116	
Age (age, mean±SD)	52.3±9.9	57.6±10.6	62.6±10.0	<0.001*
M/F	213/230 (0.9)	139/125 (1.1)	92/24 (3.8)	<0.001†
Subtype 1b (%)	208 (47.0)	146 (55.3)	70 (60.3)	0.012‡
non-1b (%)	235 (53.0)	118 (44.7)	46 (39.7)	

*One way ANOVA and †,‡Chi-square test.
*CH vs. LC vs. HCC; †CH or LC vs. HCC; ‡CH vs. LC or HCC
CH, chronic hepatitis; LC, liver cirrhosis; HCC, hepatocellular carcinoma.

Table 5. The influences of risk factors for the development of HCC

Variate	Odds ratio	95% confidence interval	*P*-value*
Age	1.081	1.056-1.106	<0.001
Male sexuality	5.749	3.329-9.930	<0.001
Liver damage†	2.895	2.183-3.840	<0.001
Subtype 1b	1.423	0.895-2.262	0.149

*Multiple logistic regression analysis; †Liver damage, non-liver cirrhosis vs. compensated liver cirrhosis vs. decompensated liver cirrhosis.
HCC, hepatocellular carcinoma.

but the difference between the groups of patients with LC and HCC was not statistically significant (Table 4).

The influence of the risk factors for the development of HCC

Age, male sexuality, and the progression of liver damage from non-LC to decompensated LC were significant risk factors for the development of HCC with odds ratios of 1.081 (95% CI 1.056-1.106), 5.749 (95% CI 3.329-9.930) and 2.895 (95% CI 2.183-3.840), respectively. HCV subtype 1b (odds ratio=1.423, 95% CI 0.895-2.262) was not likely to cause HCC more often than HCV non-1b subtypes (Table 5).

DISCUSSION

Genotype 1 is the most common HCV genotype in the United States,[25] Europe,[26] and Japan.[27] At least more than 60% of cases of chronic HCV infections are due to HCV genotype 1, but substantial differences appear to exist in the distribution of subtypes within HCV genotype 1 in these areas,[25-27] Subtype 1a is around three times as predominant as subtype 1b in the United States,[25] while subtype 1b is about three times more common than subtype 1a in Europe.[26] HCV subtype 1b (51.6%) was the most prevalent HCV genotype in this study as in reports from Europe.[26] and Japan.[27] In Korea, the proportion of HCV subtype 1b also appears to be around 50%.[8] HCV subtype 1a is very rare (around 1%)[8] in Korea as in Japan (0.0%).[27] The proportion of HCV subtype 1a was also 1.1% in this study.

The proportion of HCV genotype 2 seems not to exceed more than 20% of chronic HCV infections in the United States,[25] and Europe.[26] This study showed a much higher proportion (45.8%) of HCV genotype 2 including subtype 2a/2c, 2b, and 2 than the reports from the United States,[25] Europe,[26] and Japan (26.2%).[27] The proportion of HCV genotype 2 seems to be approximately equal to

http://dx.doi.org/10.3350/cmh.2012.18.2.219

that of the HCV subtype 1b in Korea.[8]

In this study, nine patients (1.1%) had genotype 3, which is known to be particularly prevalent in intravenous drug abusers in Europe and the United States.[7] We were not able to find any evidence of intravenous drug abuse in these patients. They were relatively young with a median age of 37 years (range, 29-55 years). This value is not listed in the table. The proportions of HCV genotype 3 in Japan (0.0%)[27] and Korea (0.4%)[8] differ greatly from those in South America (37%)[28] and South Asia (62.2%).[29] In this study, a case of HCV genotype 4 was found in a 38 year old male patient who was Vietnamese worker living in Busan. In Korea, though no study for HCV genotype 4 has ever been reported in the literature, we can easily imagine that genotype 4 is rare but does exist with some proportion due to the fact that there are already approximately 1.2 million foreign residents. HCV genotype 4 is common in the Middle East and Africa, where it is responsible for more than 80% of chronic HCV infections, and has recently spread to several European countries.[5]

Although there are still some controversies,[16-18] several studies[9,10] have demonstrated that HCV subtype 1b is more closely associated with LC and older age than non-1b subtypes in patients with chronic HCV infection. In one study,[10] patients older than 40 years were infected almost exclusively with HCV subtype 1b. This study showed that there were also trends for the proportion of HCV subtype 1b to increase with the progression of liver damage from non-LC to LC, but the proportion of HCV subtype 1b did not change with age. Namely, when we divided the patients into two groups of patients with non-LC and LC without considering the presence of HCC, the proportion of patients with chronic HCV subtype 1b infection increased significantly (P=0.006) from 47.3% in the group of patients with non-LC to 56.9% in the group of patients with LC, but although there was no statistically significant difference, the mean age of the non-LC or LC group of patients with subtype 1b was rather lower than that of the non-LC or LC group of patients with non-1b subtypes. These findings seemed to give us basis to say that HCV subtype 1b is more influential than non-1b subtypes on the progression of non-LC to LC, and has a tendency to exacerbate CH more rapidly than non-1b subtypes during the long period of chronic HCV infection.

Several studies demonstrated that HCV subtype 1b is more closely related to the development of HCC than non-1b subtypes,[10-14] but there still have been disagreement against this.[16-20] In this study, the proportions of HCV subtype 1b increased seemingly with the severity of liver disease. The proportions of HCV subtype 1b in the groups of patients with CH, LC, and HCC were 47.0%, 55.3%, and 60.3%, respectively (CH vs. LC or HCC, P=0.012), but the difference between the groups of patients with LC and HCC was not statistically significant. These findings suggest that HCV subtype 1b is more influential than non-1b subtypes on the progress of CH to LC , but not on the development of HCC from LC.

In this study, the mean age (62.6±10.0) and the ratio of males to females (92/24) in the group of patients with HCC were significantly (P<0.001) higher than those in the group of patients with CH (52.3±9.9 and 212/230) or patients with LC (57.6±10.6 and 139/125). Other studies also showed that age was closely associated with the development of HCC, and male sexuality[10,13,14] worked as the major risk factor for HCC in patients with chronic HCV infection. One study[30] demonstrated that the incidence of HCC in men is more than twice that of women even after controlling known risk factors such as chronic viral hepatitis, alcoholism, aflatoxin B1 ingestion, fatty liver disease, and inborn errors of metabolism. But the cause for male predominance in HCC development has not been identified till now. Using the multiple logistic regression analysis, we were able to make certain that the development of HCC in patients with chronic HCV infection was significantly associated with age, male sexuality, and the progression of liver damage from non-LC to decompensated LC, but not with HCV subtype 1b.

This study showed that HCV subtypes 1b (51.6%) and 2a/2c (39.5%) were the two most common HCV genotypes. The proportion of genotype 2 (2a/2c, 2b, and 2) was 45.8%. HCV subtype 1b seemed to be more influential than non-1b subtypes on the progress of CH to LC, but not on the development of HCC from LC. The development of HCC in patients with chronic HCV infection was significantly associated with age, male sexuality, and the progression of liver damage from non-LC to decompensated LC.

This study has limitations. First, it had to rely on the allowance of existing views about the patients' baseline characteristics, such as serum HCV-RNA level, body mass index, amount of alcohol consumption, and presence of diabetes mellitus which are considered to be significant risk factors predicting the development of liver cirrhosis and hepatocellular carcinoma in patients with chronic HCV infection. Second, we were not free from some errors in diagnosing the liver cirrhosis and hepatocellular carcinoma because histological confirmation was not performed in many patients.

Conflicts of Interest

The authors have no conflicts to disclose.

 http://dx.doi.org/10.3350/cmh.2012.18.2.219

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