

Relative Etiologic Role of Hepatitis B Virus and Hepatitis C Virus in Chronic Liver Diseases and Hepatocellular Carcinoma among Age-Specific Groups in Korea: the Possible Presence of Non-B, Non-C Agents

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= Abstract = **Korea is one of the endemic areas of chronic hepatitis B virus (HBV) infection. To investigate the relative etiologic role of HBV and hepatitis C virus (HCV) in chronic liver diseases (CLD) including hepatocellular carcinoma (HCC) among age-specific groups in Korea, we enrolled consecutively 673 patients with chronic active hepatitis (CAH), 677 patients with liver cirrhosis (LC) and patients with HCC who had been diagnosed in the liver unit at Seoul National University Hospital. HBsAg and anti-HCV were tested using commercially available radioimmunoassay and enzyme immunoassay kits, respectively. From this study, we were reached at suggestion for the possible presence of non-B, non-C type CLD agent(s) by exclusion method. The prevalence rates of HBsAg were 45.3%, 62.5% and 69.3% in patients with CAH, LC and HCC, respectively. The general prevalence rates of anti-HCV in patients with CAH, LC and HCC were 27.3%, 19.6% and 17%, respectively, and, however, in HBsAg-negative patients with CAH, LC and HCC those were 48.1%, 46.1% and 42.7%, respectively. The coinfection rates of HBV and HCV in patients with CAH, LC and HCC were 1%, 2.4% and 3.9%, respectively. The rates of CAH, LC and HCC patients who were negative for both HBsAg and anti-HCV and therefore, serologically classified as non-B, non-C type were 28.4%, 20.2% and 17.6%, respectively. There was a significant difference in mean age between B- and C-type, and B and non-B, non-C type patients with CAH (41.7 vs 54.5 and 50.4 years), LC (48.5 vs 60.1 and 54.9 years) and HCC (51.6 vs 60.4 and 56.1 years) ($p < 0.001$, respectively). Before the age of 50, the etiology of CAH and LC was almost exclusively HBV, while over the age of 50, the etiologic role of HCV and non-B, non-C was more predominant than that of HBV. In elderly (older than 60 years of age) patients even with HCC, HCV played an etiologic role as important as HBV.**

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In conclusion, HBV is the most common etiologic agent of CLD in Korea. However, HCV and non-B, non-C infection is a more important etiology in elderly patients with CLD older than 50 years of age.

Key Words: *Etiology, Age, HBsAg, Anti-HCV, Chronic active hepatitis, Liver cirrhosis, Hepatocellular carcinoma, Korea*

INTRODUCTION

The development of an assay for circulating antibodies against hepatitis C virus (anti-HCV) has now made possible the serological diagnosis of chronic liver disease (CLD) type C among non-A, non-B (NANB) CLD (Kuo *et al.* 1989). The anti-HCV test has confirmed that HCV is frequently involved in the patients with chronic NANB hepatitis in Western countries (Kuo *et al.* 1989; Di Bisceglie *et al.* 1989; Roggendorf *et al.* 1989) and Japan (Nishioka 1991).

In a previous study (Kim *et al.* 1992), we showed that the mean age of HBsAg-positive patients with CLD was significantly lower than that of HBsAg-negative (NANB) patients with CLD. In clinical practice, we suspected that anti-HCV-positive CLD's were more frequently observed in elderly patients.

This study was to investigate the relative etiologic role of HBV, HCV and non-B, non-C agents in CLD including hepatocellular carcinoma (HCC) among age-specific groups in Korea.

MATERIALS AND METHODS

1. Patients

We enrolled consecutively 673 patients with chronic active hepatitis (CAH), 677 patients with liver cirrhosis (LC) and 336 patients with HCC who had been diagnosed in the liver unit at Seoul National University Hospital. The demographic characteristics of the patient are shown in Table 1. The diagnosis of CAH was mostly made by liver biopsy, and that of LC by liver biopsy under peritoneoscopy and/or by clinical manifestations of portal hypertension.

The diagnosis of HCC was made by 1) presence of a mass lesion on ultrasonogram and/or CT scan of the liver with significant elevation of serum alpha-fetoprotein (AFP) levels (Lee *et al.* 1991), 2) typical angiographic findings (Kido *et al.* 1971) with or without significant elevation of AFP levels, 3) liver needle biopsy under peritoneoscopy or ultrasonography. The patients who supposedly were thought to be related to alcohol and drugs were eliminated.

2. Serological tests

The sera which had been collected at the time of diagnosis and stored at -20°C were tested for HBsAg and anti-HCV, using commercially available radioimmunoassay and enzyme immunoassay kits (AUSRIA-II and HCV EIA Abbott Laboratories, Chicago IL, respectively). Non-B, non-C type CLD was classified for those who were negative for both HBsAg and anti-HCV.

3. Statistical analysis

Statistical analyses were conducted with Student t-test and χ^2 -test using SPSS/PC+ (Microsoft Corp).

Table 1. Demographic characteristics of the patients with chronic active hepatitis (CAH), liver cirrhosis (LC) and hepatocellular carcinoma (HCC)

	CAH	LC	HCC
Number	673	677	336
Sex (M/F)	4.1:1	3.2:1	5.9:1
Mean age±SD	47.7±11.3	51.9±10.1	53.7±9.1
Range	16-78	17-81	28-83

RESULTS

1. Prevalence of HBsAg and anti-HCV, and non-B, non-C related CLD

The positive rates for HBsAg and/or anti-HCV and the negative rates for both HBsAg and anti-HCV are shown in Table 2. The general prevalence rates of anti-HCV, however, in patients with CAH, LC and HCC were 27.3%, 19.6% and 17.0%, respectively, (not shown in table), and those in HBsAg-negative patients with CAH, LC and HCC were 48.1%, 46.1% and 42.7%, respectively. The coinfection rates of both HBV and HCV in patients with CAH, LC and

HCC were 1.0%, 2.4% and 3.9%, respectively, (not shown in table). The rates of CAH, LC and HCC patients who were negative for both HBsAg and anti-HCV and therefore, serologically classified as non-B, non-C type were 28.4%, 20.2% and 17.6%, respectively.

2. Age distribution of HBsAg-, anti-HCV-positive and both negative patients

The mean age of each type of CLD is shown in Table 3. There was a significant difference in mean age between B- and C-type and B- and non-B, non-C patients with CAH, LC and HCC ($p < 0.001$, respectively). However, there was no such difference between C and non-B, non-C

Table 2. HBsAg and anti-HCV positivity in patients with chronic active hepatitis (CAH), liver cirrhosis (LC) and hepatocellular carcinoma (HCC)

	HBsAg-positive		HBsAg-negative		
	No. (% in total)*	anti-HCV(+) No. (%)**	No. (% in total)*	anti-HCV(+) No. (%)***	anti-HCV(-) No. (% in total)*
CAH (n=673)	305(45.3%)	7(2.3%)	368(54.7%)	177(48.1%)	191(28.4%)
LC (n=677)	423(62.5%)	16(3.8%)	254(37.5%)	117(46.1%)	137(20.2%)
HCC (n=336)	233(69.3%)	13(5.6%)	103(30.7%)	44(42.7%)	59(17.6%)

* : The denominator is the number of all patients with each type of CLD.

** : The denominator is the number of HBsAg-positive patients with each type of CLD.

*** : The denominator is the number of HBsAg-negative patients with each type of CLD.

Table 3. Mean ages of the patients with chronic active hepatitis (CAH), liver cirrhosis (LC) and hepatocellular carcinoma (HCC) according to serological status of HBsAg and anti-HCV

Types	Serology		CAH	LC	HCC
B	HBsAg (+)	Age (M±SD)	41.7±9.6*	48.5±9.0*	51.6±7.9*
		Range	16-73	17-74	29-71
		M/F	6.6:1	3.6:1	6.5:1
C	Anti-HCV (+)	Age (M±SD)	54.5±10.2**	60.1±7.9**	60.4±7.2**
		Range	20-78	39-81	41-75
		M/F	2.7:1	2.0:1	5.3:1
Non-B, non-C	HBsAg (-) and anti-HCV(-)	Age (M±SD)	50.4±10.0***	54.9±9.5***	56.1±11.4***
		Range	20-76	25-73	28-83
		M/F	3.2:1	3.7:1	4.4:1

p values between * and ** < 0.001

p values between * and *** < 0.001

type ($p > 0.05$). Figure 1 shows the clear difference in the age distribution between HBsAg-positive and anti-HCV-positive patients with CAH, LC and HCC, respectively; anti-HCV-positive patients in each panel were distributed at more elderly groups than HBsAg-positive patients. Figure 2 shows the relative etiologic role of HBV and HCV in each age-specific group. Before the age of 50, the etiology of CAH and LC was almost exclusively HBV, while over the age of 50, the etiologic role of HCV is more predominant than that of HBV. In patients older than 60 years of age even with HCC, HCV played an etiologic role as important as HBV.

DISCUSSION

In this study, we could clearly demonstrate the etiologic profile of chronic liver diseases including HCC in Korea; HBV is the most common cause of chronic liver diseases and HCV also played a significant etiologic role in CLD in Korea. The prevalence rates of anti-HCV-positivity in HBsAg-negative (NANB type) patients with CLD observed in the present study was lower than those observed in European countries and Japan where HBV infection is relatively less prevalent and, was comparable to those reported in Taiwan which is one of the HBV endemic areas. The reason why the anti-HCV positive rate in each CLD in HBV endemic areas was lower than that in less prevalent areas of HBV still remains to be further investigated. One explanation may be that a significant proportion of HBsAg-negative (therefore, serologically classified as NANB) patients in HBV endemic areas might be HBV related, which has been proven by the presence of HBV DNA in their sera in our previous study (Lee *et al.* 1992).

Chuang (Chuang *et al.* 1992) in Taiwan as well as Bruix (Bruix *et al.* 1989) in Spain observed a higher prevalence of coinfection of HBsAg and anti-HCV in patients with HCC than in patients with other CLD's; thus, they reported that the patients coinfecting with HBV and HCV were more likely to develop HCC than patients

with either agent alone, suggesting the combined oncogenic action of both viruses. However, the low rate of coinfection of HBV and HCV (3.9% of total patients with HCC) observed in the present study did not support their hypothesis.

One fifth to one fourth of all CLD patients had neither HBsAg nor anti-HCV reactivity, thus thought to be and classified as non-B, non-C type. The negative reaction may be due to lack of sensitivity of the test currently available for HBV or HCV. To assess the etiologic role of HBV and HCV in non-B, non-C CLD's, detection of serum HBV DNA and HCV RNA using (reverse-transcriptase) polymerase chain reaction is warranted. However, we can not now exclude the possible involvement of an unveiled hepatitis virus in these patients.

The present study proved our hypothesis to be true that the mean age of HBsAg-positive patients with each type of CLD is younger than that of anti-HCV-positive. A possible explanation for the difference is that chronic NANB hepatitis was a much slower process than chronic hepatitis B (Okuda *et al.* 1984), and CLD, NANB appeared clinically indolent even if histologically manifested (Alter 1990); therefore, HCV infection took longer to lead to advanced disease which was clinically manifested. Another explanation might be that it is due to the acquisition of the infection at different ages; HBV infection is mostly acquired vertically in the perinatal period (Nishioka 1984) and HCV infection sporadically during adult life (Dienstag and Alter 1986). However, the cause of the difference still remains to be clarified.

Of interest in this study is that HCV played a no less important etiologic role than HBV in elderly patients (over the age of 50) even in a hepatitis B endemic area. Before the age of 50, the etiology of CAH and LC was almost exclusively HBV, while over the age of 50, the etiologic role of HCV is more predominant than that of HBV. In elderly (older than 60 years of age) patients even with HCC, HCV played an etiologic role as important as HBV. This finding

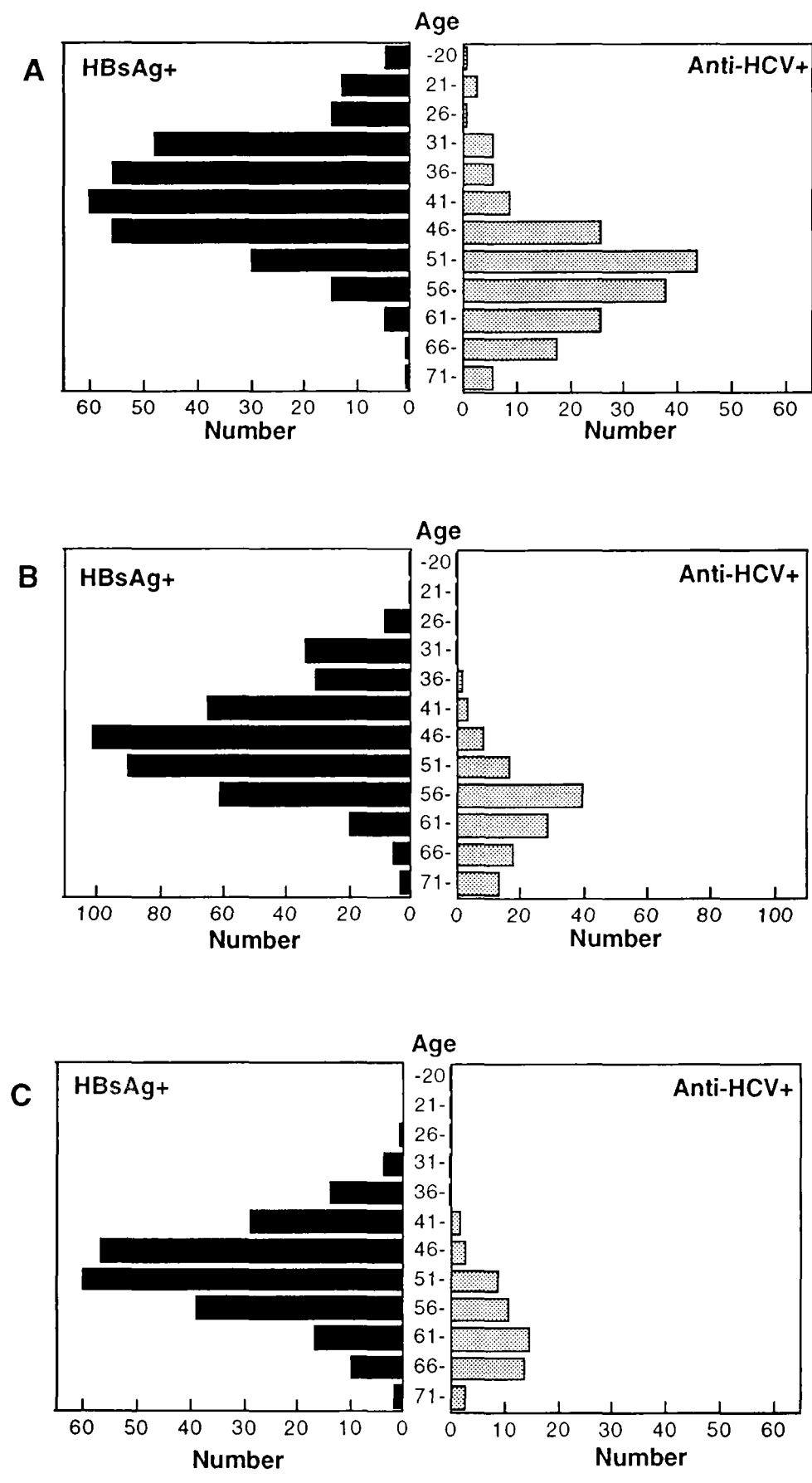


Fig. 1. Comparison of the age distribution between HBsAg-positive and anti-HCV-positive patients in each chronic liver disease. A: chronic active hepatitis, B: liver cirrhosis, C: hepatocellular carcinoma.

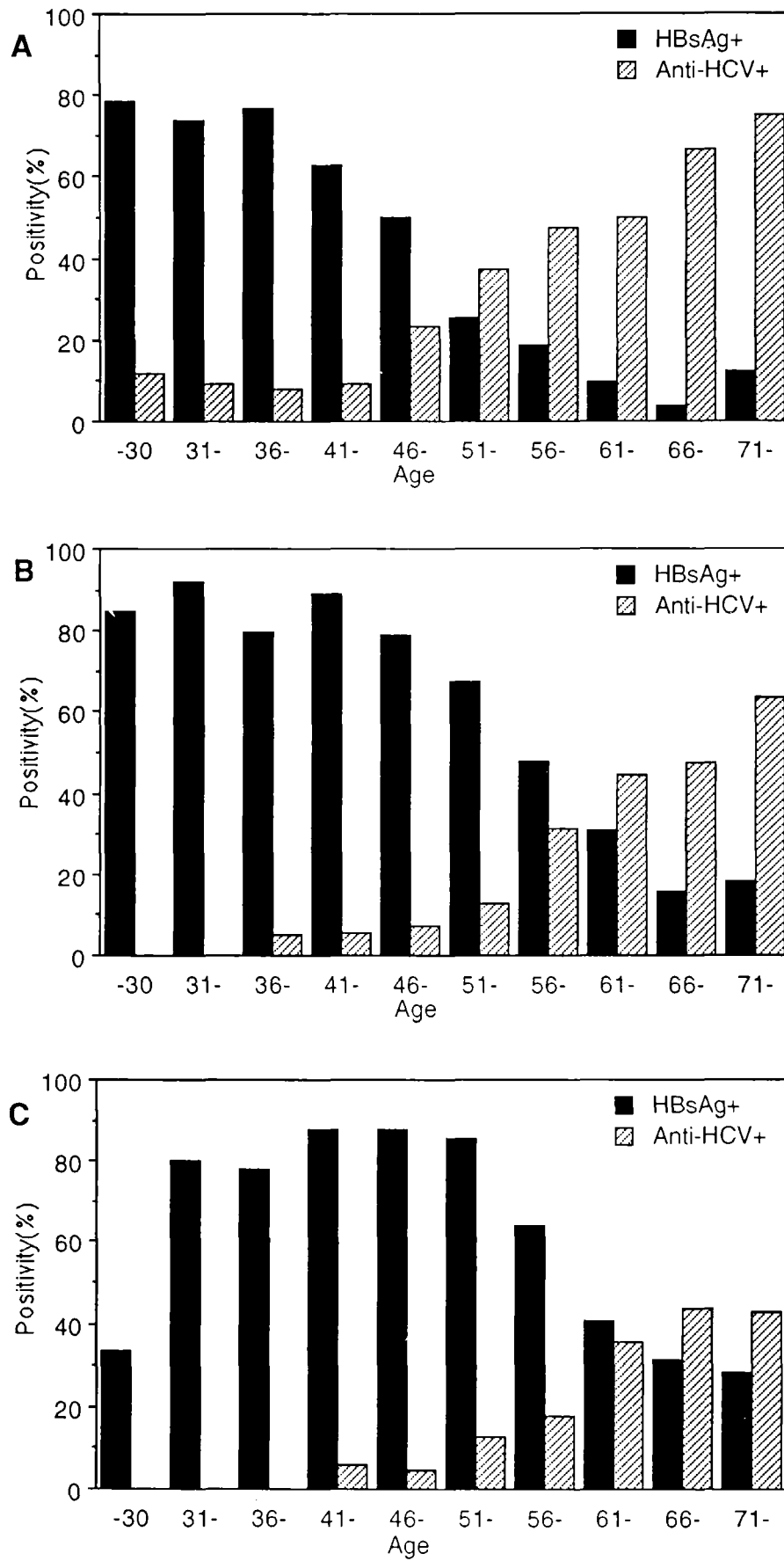


Fig. 2. Comparison of the positivity rate of HBsAg and anti-HCV in age specific groups in each chronic liver disease. A: chronic active hepatitis, B: liver cirrhosis, C: hepatocellular carcinoma.

observed in Korea will possibly be proven to be general by further studies in other hepatitis B endemic areas such as Taiwan.

In conclusion, HBV is the most common etiologic agent of CLD in Korea. However, HCV infection is a more important etiology in elderly patients with CLD older than 50 years of age. Furthermore, this study would suggest that one should look at the other agent(s) when there are no HBV or HCV markers.

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