

HBsAg⁺ and HBsAg⁻ Chronic Active Hepatitis, Liver Cirrhosis and Hepatocellular Carcinoma in Korea: Prevalence and Difference in Age Distribution †

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= Abstract = Korea is one of the endemic areas of hepatitis B virus infection. In clinical practice, we have suspected that HBsAg⁺ patients with chronic liver disease (CLD) are younger than HBsAg⁻ patient. In order to determine the prevalence of HBV infection more clearly in patients with CLD and to investigate the difference in age-specific distribution between HBsAg⁺ and HBsAg⁻ patients, we consecutively enrolled 3185 patients with chronic active hepatitis (CAH), 1919 patients with liver cirrhosis (LC) and 628 patients with hepatocellular carcinoma (HCC) who were diagnosed in the liver unit at Seoul National University Hospital from 1973 to 1991. HBsAg was positive in 61.4%, 67.8% and 68.9% of patients with CAH, LC and HCC, respectively. In comparison, anti-HBs was positive only in 16.4%, 14.4% and 11.6% of patients with CAH, LC and HCC, respectively. Among HBsAg⁻ patients, patients with isolated antibody to HBe were most common; 15.6%, 13.9% and 15.4% in CAH, LC and HCC, respectively. Almost all of the patients with CAH, LC and HCC (93.4%, 96.1% and 95.9%, respectively) were positive for any of HBV serological markers. The mean ages of HBsAg⁺ and HBsAg⁻ patients with CAH, LC and HCC were 38.0 and 45.8, 45.6 and 51.2, and 49.5 and 55.5 years, respectively; the differences between HBsAg⁺ and HBsAg⁻ patients were statistically significant in each CLD ($p < 0.01$). When HBsAg⁻ groups were subdivided into 4 smaller subgroups according to HBV antibody profiles, such differences were not demonstrated among 4 HBsAg⁻ subgroups. Intervals in years between CAH and LC and between LC and HCC were not different according to HBsAg status in the serum. We concluded that the prevalence of present and past HBV infection in patients with CLD in Korea was extremely high, and that HBsAg⁺ patients developed CLD at a younger age than HBsAg⁻ patients, the reason for which remains to be established.

Key Words: *Hepatitis B viral markers, Hepatitis B surface antigen, Chronic active hepatitis, Liver cirrhosis, Hepatocellular carcinoma, Korea*

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INTRODUCTION

Korea is one of the endemic areas of hepatitis B virus (HBV) infection: HBsAg, anti-HBs and anti-HBe were positive in 6.6%, 31.9% and 41.6% of the general population

(Hong *et al.* 1982). Among patients with acute viral hepatitis, 60.3% were classified as type B (Lee *et al.* 1990). The positive rates for HBsAg in patients with chronic active hepatitis (CAH) and liver cirrhosis (LC) were reported to be 66~85% and 45~66%, respectively (Kang *et al.* 1983; Lee *et al.* 1985; Suh *et al.* 1982), and 69.3~75% and 93.8~100% of the patients with hepatocellular carcinoma (HCC) were reported to be positive for HBsAg and for any of HBV serological markers, respectively (Kang *et al.* 1983; Lee *et al.* 1985). This wide range of positive rates of HBV serological markers in these studies may result from the small number of patients investigated. A study which includes a large number of patients is needed to define more precisely the prevalence of present and past HBV infection in Korea.

In clinical practice, we have suspected that the mean age of the HBsAg⁺ patients with chronic liver disease (CLD) is lower than that of HBsAg⁻ patients. However, this opinion has not yet been demonstrated to be correct.

In order to determine the prevalence of each profile of HBV serological markers more clearly in patients with CLD and to investigate the difference in mean age between patients with HBsAg⁺ and HBsAg⁻ CLD, we registered a large number of patients with CAH, LC and HCC.

MATERIALS AND METHODS

1. Patients

We enrolled consecutively 3185 patients with CAH, 1919 patients with LC and 628 patients with HCC who had been diagnosed in the liver unit at Seoul National University Hospital from 1973 to 1991. Patients with a social history of excessive alcohol ingestion were excluded. Demographic characteristics of the patient are shown in Table 1.

The diagnosis of CAH was made mostly by liver biopsy, and that of LC by liver biopsy under peritoneoscopy and/or by accompanying clinical findings of portal hypertension. The diagnosis of HCC was made by 1) presence of mass lesion on ultrasonogram and/or CT

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

	CAH	LC	HCC
Number	3185	1919	628
Sex : M/F	3.5	2.6	5.9
Mean age ± SD	41 ± 0.2	47.4 ± 0.4	51.4 ± 9.7
Range (years)	(11~76)	(18~77)	(19~79)

scan of the liver with significant elevation of serum alpha-fetoprotein (AFP) levels (Lee *et al.* 1991), 2) typical angiographic findings, 3) liver needle biopsy under peritoneoscopy or ultrasonography with or without significant elevation of AFP levels.

2. Serological Tests

The sera which had been collected on admission were tested for HBsAg, anti-HBc, and anti-HBs, using commercially available radioimmunoassay kits (AUSRIA-II, CORAB, and AUSAB Abbott-Laboratories, Chicago IL, respectively).

3. Statistical analysis

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

RESULTS

1. Prevalence of each profile of HBV serological markers.

This is shown in Table 2. HBsAg was positive in 61.4%, 67.8% and 68.9% of patients with CAH, LC and HCC, respectively. In comparison, anti-HBs was positive only in 16.4%, 14.4% and 11.6% of patients with CAH, LC and HCC, respectively. Among HBsAg⁻ patients, patients with isolated antibody to HBc were most common; 15.6%, 13.9% and 15.4% in CAH, LC and HCC, respectively. Almost all of the patients with CAH, LC and HCC (93.4%, 96.1% and 95.9%, respectively) were positive for any of HBV serological markers.

Table 2. Prevalence of each profile of HBV serological markers in patients with chronic active hepatitis(CAH), liver cirrhosis(LC) and hepatocellular carcinoma(HCC)

HBV markers			CAH	LC	HCC
HBsAg	anti-HBc	anti-HBs	No.(%)	No.(%)	No.(%)
+	+	-	1,956(61.4)	1,302(67.8)	433(68.9)
-	+	-	498(15.6)	268(13.9)	97(15.4)
-	+	+	440(13.8)	254(13.2)	65(10.5)
-	-	+	83(2.6)	23(1.2)	7(1.1)
-	-	-	208(6.6)	72(3.9)	26(4.1)
Total			3,185(100)	1,919(100)	628(100)

2. Age distribution of HBsAg⁺ and HBsAg⁻ patients

The mean ages of HBsAg⁺ and HBsAg⁻ patients with CAH, LC and HCC were 38.0 and 45.8, 45.6 and 51.2, and 49.5 and 55.5 years, respectively; the difference in mean age between HBsAg⁺ and HBsAg⁻ patients was statistically significant in each CLD (P < 0.01). When the HBsAg⁻ group was subdivided into 4 smaller subgroups according to HBV antibody profiles, a similar difference was also found between the HBsAg⁺ group and each HBsAg⁻ subgroup. However, such difference was not demonstrated among the 4 HBsAg⁻ subgroups (Table 3). The difference in age-specific distribution between HBsAg⁺ and HBsAg⁻ patients is clearly depicted in Figure 1. Intervals in years between CAH and LC and between LC and HCC in HBsAg⁻ patients were no longer than those in HBsAg⁺ patients (Table 4).

DISCUSSION

To our knowledge, this is the largest Korean series studied for HBV serological markers. We believe that the sampling procedure adopted and the large size of the sample studied provide a good estimate of present and past HBV infection in Korean patients with CLD including HCC. The results reported here confirm that the prevalence of present and past HBV infection among Korean

Table 3. Mean ages of the patients with chronic active hepatitis(CAH), liver cirrhosis (LC) and hepatocellular carcinoma (HCC) according to each profile of HBV serological markers

HBV markers			CAH	LC	HCC
HBsAg	anti-HBc	anti-HBs	mean±SD	mean±SD	mean±SD
+	+	-	38.0±9.9	45.6±11.3	49.5±8.6
-	+	-	45.8±10.1*	51.2±10.0*	55.9±8.7*
-	+	+	46.2±10.2*	51.0±9.6*	56.1±9.8*
-	-	+	46.2±10.1*	52.1±8.2*	56.6±7.2*
-	-	-	45.0±10.7*	50.9±10.6*	52.4±11.7*

* p<0.01 : difference between HBsAg⁺ group and each HBsAg⁻ subgroups

Table 4. Difference in mean age between chronic active hepatitis(CAH) and liver cirrhosis(LC) and between LC and hepatocellular carcinoma(HCC)

Interval between	HBsAg	
	+	-
CAH and LC (years)	7.6	5.3
LC and HCC (years)	3.9	3

patients with CLD was extremely high (about 95%). The positive rates of HBsAg in our patients with HCC (68.9%) was in between that in Taiwan (80%) where the rate of chronic HBsAg carriers was as high as 15% to 17.8% (Tong *et al.* 1971; Sung *et al.* 1976; Hsu *et al.* 1983) and that in Japan (21~31.4%) where it was as low as 2% (Tanaka *et al.* 1991; Tobe *et al.* 1987).

This study also confirms our hypothesis that HBsAg⁺ patients develops CLD at a younger age than HBsAg⁻ patients. Before the age of 50, the etiologic agent of the majority of the patients with CAH, LC and HCC was HBV. In contrast, over the age of 60, the etiologic role of non-B was predominant over HBV. The mean age of 45.6 years for HBsAg⁺ LC in Korea was comparable to that of 44 years for HBsAg⁺ LC in Japan (Tanaka *et al.* 1987), and the mean age of 49.5 years for HBsAg⁺ HCC in Korea was also

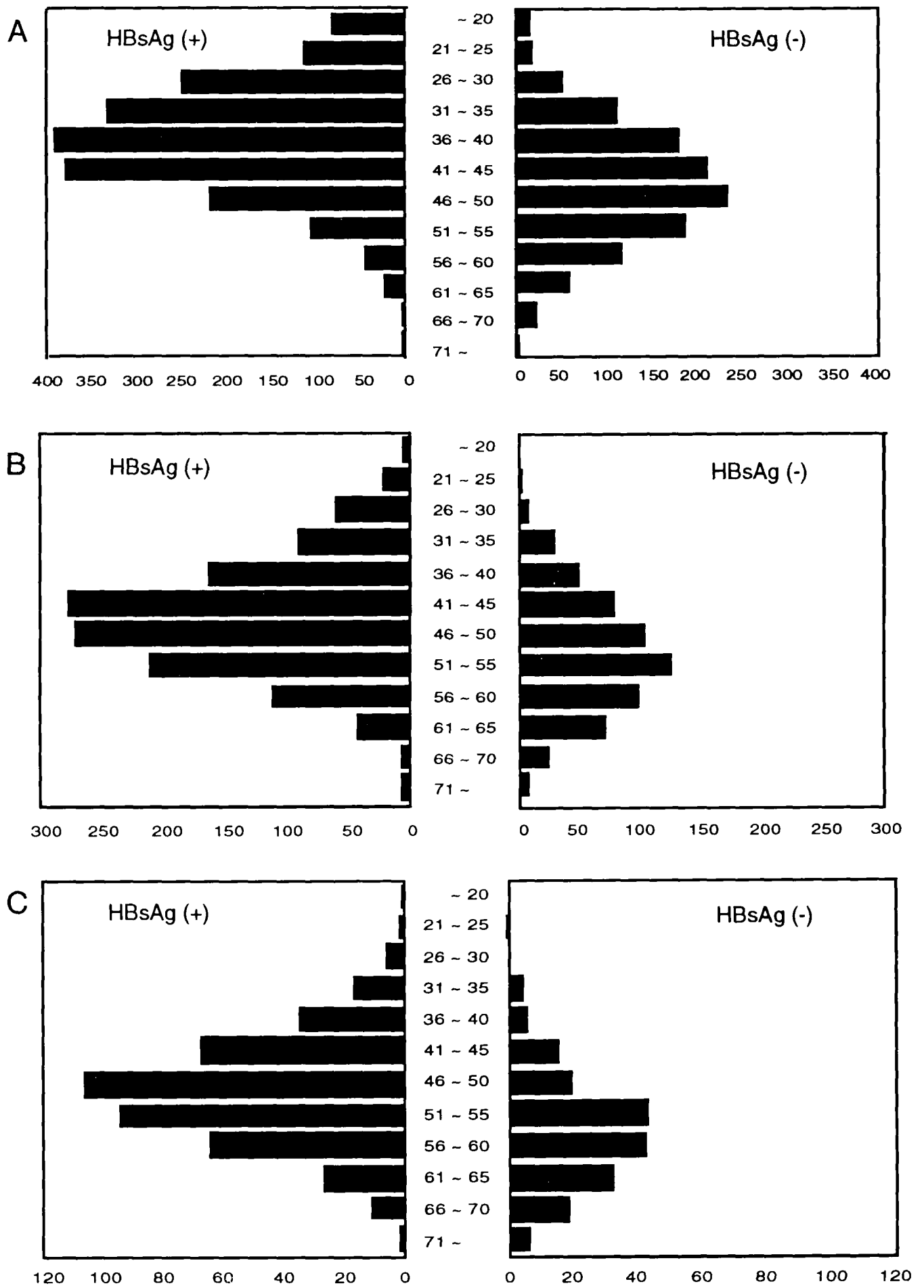


Fig. 1. Age-specific distribution of HBsAg⁺ and HBsAg⁻ patients with chronic active hepatitis(A) liver cirrhosis(B) and hepatocellular carcinoma(C).

comparable to that of 51.3 years for HBsAg⁺ HCC in Japan (Watanabe *et al.* 1991); thus, the mean age of onset of LC and HCC appears to be determined by the etiologic agent rather than geographic area or race. Therefore, the observation that LC and HCC developed at a younger age in Korea (47.4 and 51.4 years, respectively) than in Japan (49 and 57.4 years, respectively; Tanaka *et al.* 1987; Tobe *et al.* 1987) may be attributed to the higher prevalence of HBsAg⁺ LC and HCC in Korea than in Japan.

Okuda *et al.* (1984) suggested a possible explanation for the significant difference in the mean age of onset between HBsAg⁺ and HBsAg⁻ CLD patients; It was that chronic NANB hepatitis was a much slower process than chronic hepatitis B. However, the intervals in years between CAH and LC and LC and HCC in HBsAg⁻ patients were similar to HBsAg⁺ patients, or rather short in HBsAg⁻ patients in the present study, suggesting that Okuda's explanation might not be correct. It may be due to the acquisition of the infection at a different time; HBV infection might be mostly acquired in the perinatal period and non-B infection in childhood or adult life. However, the cause of this difference still remains to be clarified.

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