

## Seroprevalence of anti-HAV among patients with chronic viral liver disease

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Received: August 14, 2010 Revised: October 15, 2010

Accepted: October 22, 2010

Published online: January 14, 2011

**RESULTS:** The overall prevalence of IgG anti-HAV was 86.61% (854/986) in patients with chronic liver disease and was 88.13% (869/986) in age- and gender-matched patients from the Center for Health Promotion. The anti-HAV prevalence was 80.04% (405/506) in patients with chronic hepatitis B, 86.96% (20/23) in patients with chronic hepatitis C, 93.78% (422/450) in patients with HBV related liver cirrhosis, and 100% (7/7) in patients with HCV related liver cirrhosis. The anti-HAV prevalence according to the decade of age was as follows: 20s (6.67%), 30s (50.86%), 40s (92.29%), 50s (97.77%), and 60s (100%). The anti-HAV prevalence was significantly higher in patients older than 40 years compared with that in patients younger than 40 years of age. Multivariable analysis showed that age  $\geq$  40 years, female gender and metropolitan cities as the place of residence were independent risk factors for IgG anti-HAV seropositivity.

**CONCLUSION:** Most Korean patients with chronic liver disease and who are above 40 years of age have already been exposed to hepatitis A virus.

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**Key words:** Chronic hepatitis B; Chronic hepatitis C; Hepatitis A virus; Korea; Seroprevalence

**Peer reviewers:** Fernando Fornari, MD, Department of Gastroenterology, Universidade de Passo Fundo, Rua Teixeira Soares, 817, 99010080 Passo Fundo, Brazil; Fen Liu, MD, University of Minnesota, 6155 Jackson Hall, 321 Church Street SE, Minneapolis, MN 55455, United States

Cho HC, Paik SW, Kim YJ, Choi MS, Lee JH, Koh KC, Yoo BC, Son HJ, Kim SW. Seroprevalence of anti-HAV among patients with chronic viral liver disease. *World J Gastroenterol* 2011; 17(2): 236-241 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v17/i2/236.htm> DOI: <http://dx.doi.org/10.3748/wjg.v17.i2.236>

### Abstract

**AIM:** To investigate the current seroprevalence of hepatitis A virus (HAV) antibodies in patients with chronic viral liver disease in Korea. We also tried to identify the factors affecting the prevalence of HAV antibodies.

**METHODS:** We performed an analysis of the clinical records of 986 patients (mean age:  $49 \pm 9$  years, 714 males/272 females) with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection who had undergone HAV antibody testing between January 2008 and December 2009.

## INTRODUCTION

Hepatitis A virus (HAV) is an epidemiologically important virus with a worldwide distribution and causes acute hepatitis in humans. This virus has been responsible for numerous disease outbreaks resulting from close personal contact or sexual contact<sup>[1-3]</sup>, contaminated food or water<sup>[3-7]</sup>, injection drug use<sup>[8,9]</sup> and other modes of transmission<sup>[8,10]</sup>.

The pattern of this disease includes infection during early childhood followed by life-long immunity<sup>[11]</sup>. When acquired in childhood, HAV is a very benign disease, over 70% of patients are asymptomatic and fulminant liver failure is extremely rare<sup>[12,13]</sup>. When the infection occurs in adulthood, a much more prolonged course is seen and the rate of jaundice and fulminant liver failure is much higher<sup>[12-14]</sup>.

During recent decades, due to improvements in sanitation and hygiene, the age of infection by this virus has shifted from early childhood to adolescence or even later<sup>[11,15,16]</sup>. Although the overall case-fatality rate of acute HAV among persons of all ages is only 0.01%-0.3%<sup>[17-19]</sup>, it is higher (1.8%) among adults who are 50 years of age or older<sup>[19]</sup>. More importantly, acute HAV superinfection causes severe liver disease, acute liver failure and even higher mortality rates in patients with underlying chronic liver disease (CLD). Numerous studies have identified CLD as a risk factor for fulminant hepatitis and death from acute HAV infection<sup>[7,20-29]</sup>.

The aim of this study was to investigate the current seroprevalence of HAV antibodies (anti-HAV) in patients with chronic viral liver disease in South Korea. We also tried to determine the age-specific seroprevalence in these patients to assess whether vaccination against HAV is necessary in all patients who have underlying viral liver diseases, and to determine the factors that affect IgG anti-HAV seropositivity.

## MATERIALS AND METHODS

### *Study design, population, and collection of data*

We identified a total of 986 patients with chronic viral liver disease who had undergone HAV antibody testing between June 2008 and December 2009 at the Samsung Medical Center, Seoul, South Korea. The inclusion criteria consisted of hepatitis B virus (HBV) surface antigen (HBsAg) positivity or hepatitis C virus (HCV) antibodies (anti-HCV) and HCV RNA positivity in more than two tests for at least 6 mo. Patients with human immunodeficiency virus infection and a past medical history of HAV vaccination were excluded from this study.

The status of underlying liver disease was classified into chronic hepatitis and liver cirrhosis (LC). The diagnosis of LC was made if any one of the following findings was met: (1) compatible intraoperative gross findings or histologically compatible findings; (2) evidence of portal hypertension in patients with liver disease; and (3) compatible radiologic findings and platelet counts less than  $100 \times 10^9/L$ .

During the same period, 986 age- and gender-matched patients from the Center for Health Promotion were selected as the control group by one-to-one matching, and the study was statistically powered at 89%. There was no loss of subjects in the case group. Patients from the Center for Health Promotion who tested positive for HBsAg or anti-HCV and had a medical history of liver disease were excluded.

### *Laboratory procedures*

Commercially available immunoassays (Anti-HAV IgG IRMA kit, North Institute of Biological Technology, Beijing, China; ARCHITECT HBsAg assay, Abbott Laboratories, Sligo, Ireland; ADVIA Centaur HCV assay, Siemens Healthcare Diagnostics, Los Angeles, CA, USA) were used to detect IgG anti-HAV, HBsAg and anti-HCV, respectively. The HCV RNA was amplified by RNA PCR and hybridization methods (COBAS® AmpliCor HCV test version 2.0, Roche Molecular Systems, Branchburg, NJ, USA, lower limit of detection 50 IU/mL).

### *Statistical analysis*

The Cochran-Armitage trend test was used to assess the association between age and seropositivity rate for anti-HAV. McNemar's test was used to compare the seropositivity rate for anti-HAV between patients with CLD and patients from the Center for Health Promotion. Categorical variables were compared with the  $\chi^2$  test. Binary logistic regression analysis was used to determine the relationship between the variables and seropositivity for anti-HAV.

*P* values < 0.05 were considered statistically significant and Bonferroni's method was used to correct for inflated type I error due to multiple testing. All the statistical analyses were run on SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

### *Ethical considerations*

The institutional review board of Samsung Medical Center approved this retrospective study.

## RESULTS

### *Patient demographics*

The patient characteristics are detailed in Table 1. The mean age of the patients was 49 years (range: 20-80 years) and the vast majority of patients were over 40 years old (84%). A male preponderance (72.41%) was observed and the vast majority of patients had chronic viral hepatitis B (51.32%) and HBV related LC (45.64%). A relatively large proportion of the patients were from Seoul, the capital of South Korea (39.45%). The overall prevalence of IgG anti-HAV in patients with CLD was 86.61% (854/986).

### *The prevalence of IgG anti-HAV according to age*

When the study participants were classified by decade of age into five groups, from 20s to more than 60 years old, the anti-HAV seroprevalence was 6.67% and 50.86% in

Table 1 Patient characteristics

Variable	n (%)
Mean age (yr, range)	49 ± 9 (20-80)
Gender	
Female	272 (27.59)
Male	714 (72.41)
Chronic liver disease	
Chronic viral hepatitis B	506 (51.32)
Chronic viral hepatitis C	23 (2.33)
HBV related liver cirrhosis	450 (45.64)
HCV related liver cirrhosis	7 (0.71)
Place of residence	
Seoul	389 (39.45)
Gyeonggi-do	274 (27.79)
Metropolitan cities	101 (10.24)
Other provinces	223 (22.62)
Prevalence of IgG anti-HAV	854 (86.61)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HAV: Hepatitis A virus.

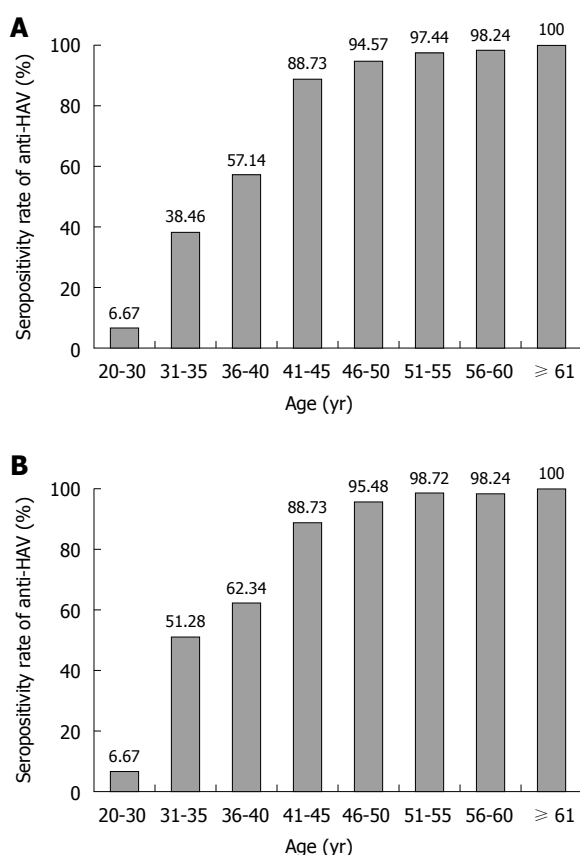


Figure 1 Prevalence of IgG anti-hepatitis A virus according to age in patients with chronic viral liver disease (A) and in age- and gender-matched patients from the Center for Health Promotion (B). HAV: Hepatitis A virus.

the patients in their 20s and 30s, respectively. The positivity rate for anti-HAV in the patients in their 40s, 50s and 60s was 92.29%, 97.77% and 100%, respectively. The prevalence of IgG anti-HAV in patients with CLD, and as divided by 5-year age intervals, is shown in Figure 1A. The seropositivity rate for anti-HAV increased gradually as age increased ( $P < 0.001$ ). The anti-HAV prevalence was significantly higher in patients older than 40 years compared

Table 2 Prevalence of IgG anti-hepatitis A virus in patients with hepatitis B virus *vs* those with hepatitis C virus infection n (%)

Age (yr)	Anti-HAV/HBV	Anti-HAV/HCV
20-30	3/43 (6.98)	0
31-40	58/112 (51.79)	0/2 (0)
41-50	325/351 (92.59)	6/7 (85.71)
51-60	378/387 (97.67)	12/12 (100)
≥ 61	63/63 (100)	9/9 (100)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HAV: Hepatitis A virus.

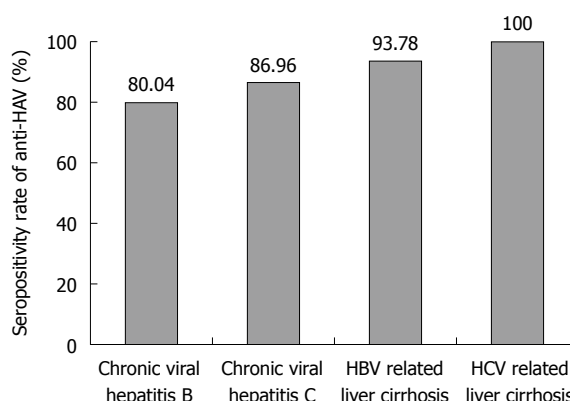


Figure 2 Prevalence of IgG anti-hepatitis A virus according to the status of chronic viral liver disease. HAV: Hepatitis A virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

with those patients younger than 40 years of age (94.95% *vs* 33.58%, respectively,  $P < 0.001$ ).

The prevalence of IgG anti-HAV according to age in the age- and gender-matched patients from the Center for Health Promotion is shown in Figure 1B. The overall prevalence of anti-HAV was 88.13% (869/986) and the seropositivity rate for anti-HAV increased gradually as age increased ( $P < 0.001$ ). There was no significant difference in the anti-HAV seroprevalence between patients with CLD and those from the Center for Health Promotion ( $P = 0.141$ ).

### The prevalence of IgG anti-HAV according to the etiology and status of liver disease

The overall prevalence of anti-HAV was 86.51% in the 956 patients with chronic HBV infection, and it was 90% in the 30 patients with chronic HCV infection. There was no statistically significant difference in seropositivity for anti-HAV between the patients with HBV infection and those with HCV infection ( $P = 0.582$ ). For the HBsAg-positive patients, the anti-HAV prevalence in each group divided by the decade of age increased gradually as age increased, which was similar for all the patients (Table 2).

The prevalence of IgG anti-HAV according to the status of CLD is shown in Figure 2. The anti-HAV seroprevalence was 80.04% (405/506) in patients with chronic hepatitis B, 86.96% (20/23) in patients with chronic hepatitis C, 93.78% (422/450) in patients with HBV related LC and 100% (7/7) in patients with HCV related LC.

**Table 3** Prevalence of IgG anti-hepatitis A virus according to gender, the status of liver disease and the place of residence

Characteristics	Anti-HAV positivity, <i>n</i> (%)	<i>P</i> value
Sex		0.049
Male	609/714 (85.29)	
Female	245/272 (90.07)	
Status of liver disease		< 0.001
Chronic viral hepatitis	425/529 (80.34)	
Liver cirrhosis	429/457 (93.87)	
Place of residence		< 0.001
Seoul	311/389 (79.95)	
Gyeonggi-do	241/274 (87.96)	
Metropolitan cities	96/101 (95.05)	
Other provinces	206/223 (92.38)	

HAV: Hepatitis A virus.

**Table 4** Factors affecting seropositivity for IgG anti-hepatitis A virus on the multivariable analysis

Characteristics	Anti-HAV positivity, <i>n</i> (%)	OR (95% CI)	<i>P</i> value
Age ( $\geq 40$ yr)	809/852 (94.95)	33.44 (20.14-55.52)	< 0.001
Female	245/272 (90.07)	2.07 (1.16-3.71)	0.014
Etiology			0.487
HBV	827/956 (86.51)	1	
HCV	27/30 (90)	0.61 (0.15-2.47)	
Status of liver disease			0.075
Chronic viral hepatitis	425/529 (80.34)	1	
Liver cirrhosis	429/457 (93.87)	1.64 (0.95-2.82)	
Place of residence			0.035
Seoul	311/389 (79.95)	1	
Gyeonggi-do	241/274 (87.96)	1.51 (0.86-2.66)	0.153
Metropolitan cities	96/101 (95.05)	4.11 (1.37-12.35)	0.012
Other provinces	206/223 (92.38)	1.84 (0.93-3.65)	0.080

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HAV: Hepatitis A virus; OR: Odds ratio; CI: Confidence interval.

**Factors affecting the seropositivity of IgG anti-HAV**

The anti-HAV prevalence according to gender, the status of liver disease and place of residence is shown in Table 3. Anti-HAV was more frequently detected in female patients (90.07%) than in male patients (85.29%,  $P = 0.049$ ). As for the status of liver disease, anti-HAV antibody was more frequently detected in patients with LC (93.87%) than in those with chronic hepatitis (80.34%,  $P < 0.001$ ). As for the place of residence, anti-HAV antibody was less frequently detected among patients who lived in Seoul or Gyeonggi-do (79.95%-87.96%) than among those living in metropolitan cities or other provinces (92.38%-95.05%,  $P < 0.001$ ).

Multivariable analysis of the factors for anti-HAV seropositivity is shown in Table 4. Age  $\geq 40$  years ( $P < 0.001$ ), female gender ( $P = 0.014$ ) and metropolitan cities as the place of residence ( $P = 0.012$ ) were independent risk factors for IgG anti-HAV seropositivity.

**DISCUSSION**

The epidemiological pattern of HAV infection is cur-

rently changing in many developing countries. An improved socioeconomic status, more sanitary conditions and better hygiene practices have reduced the incidence of HAV infection, and the age-specific HAV seroprevalence in the general population has steadily decreased. The decrease in HAV infection in young adults has resulted in a reduction in individuals with protective antibody and increased hepatitis A in the adult population. In Korea, symptomatic hepatitis A has been gradually increasing since the mid-1990s, with a tendency toward an increase in the mean age and disease severity<sup>[30-35]</sup>.

A number of studies have suggested that the clinical course of HAV infection is more severe in patients with CLD<sup>[7,20-29]</sup>. Mortality in patients with HBsAg was found to be significantly higher than that in patients without HBsAg in an outbreak of HAV infection in Shanghai<sup>[23]</sup>, and an analysis of HAV associated deaths in the United States revealed a higher rate of fatality in HBV carriers than in patients without HBV<sup>[24]</sup>. Moreover, patients with HCV infection were reported to experience HAV associated fulminant hepatic failure more often than those patients without CLD. In a prospective cohort study of adults with HCV infection, Vento *et al*<sup>[31]</sup> reported that 41.2% of patients with acute HAV superinfection developed acute liver failure and 35.3% died.

In our study, the overall seroprevalence of IgG anti-HAV in the 986 Korean patients with chronic viral liver disease was 86.61%. When the study participants were classified by the decade of age, the anti-HAV seroprevalence was 6.67%, 50.86%, 92.29%, 97.77% and 100% in patients in their 20s, 30s, 40s, 50s and 60s, respectively. These results are consistent with recent Korean studies<sup>[28,29]</sup>. The anti-HAV prevalence was significantly higher in patients older than 40 years compared with those younger than 40 years of age (94.95% *vs* 33.58%, respectively). These data indicate that most patients with chronic viral liver diseases and who are above 40 years of age have already been exposed to HAV infection, and have naturally acquired immunity against HAV. Hence, vaccination against HAV should be considered in young anti-HAV-negative patients.

In the present study, we expected the seroprevalence of anti-HAV to be higher in patients with CLD than in those from the Center for Health Promotion, considering the relatively low socioeconomic status of the CLD patients. However, there was no statistically significant difference in anti-HAV seroprevalence between the two groups (86.61% *vs* 88.13%, respectively,  $P = 0.141$ ). This finding may indicate that the immune response to HAV infection is not altered by chronic infection with either HBV or HCV. This result is also consistent with the results of the multivariable analysis in our study.

As shown in the multivariable analysis and Figure 1A, patient age was the most important factor for determining the seropositivity rate of IgG anti-HAV. Although anti-HAV was more frequently detected in patients with LC than in those with chronic viral hepatitis (93.87% *vs* 80.34%, respectively), this was probably attributable to age when considering the results of the multivariable analysis.



Female patients had a relatively higher rate of HAV seropositivity. This finding might be explained by the fact that female subjects in Korea have a larger number of social and household contacts and so probably have more exposure to HAV. We also observed significant differences among the places of residence. The lowest seroprevalence was observed in Seoul, the largest and most urbanized city in Korea, and the highest was in the provinces, with a more rural way of life. Such differences in seroprevalence might well be attributed to the vast variations in living conditions.

The current study has a couple of limitations. First, this is a retrospective study and the available epidemiological data on HAV infection is limited. Socioeconomic characteristics, including the educational level, salary, the number of siblings, the type of residence, the water supply, *etc.*, were not included in this study. Although multivariable analysis of the seropositivity of anti-HAV was carried out with relatively limited variables, the results in the present study may not be applicable to all patients with CLD. Second, although the current study included a large number of CLD patients, it was performed at a single medical center. Therefore, the patients may not be representative of the whole population of Korea. We also used data from the Center for Health Promotion and these patients may not be representative of the general Korean population without CLD when considering the fact that patients with a relatively higher level of socioeconomic status visit the Center for Health Promotion.

In conclusion, the overall prevalence of IgG anti-HAV in Korean patients with chronic viral liver disease was 86.61%, and most patients who are above 40 years of age have already been exposed to HAV. Therefore, vaccination against HAV should be considered, particularly for young anti-HAV-negative patients with chronic liver disease.

## COMMENTS

### Background

An improved socioeconomic status, more sanitary conditions and better hygiene practices have reduced the incidence of hepatitis A virus (HAV) infection. In Korea, symptomatic hepatitis A has been gradually increasing since the mid-1990s, with a tendency toward an increase in the mean age and disease severity. Acute HAV superinfection causes severe liver disease, acute liver failure and even higher mortality rates in patients with underlying chronic liver disease.

### Research frontiers

Identifying the current seroprevalence of HAV antibodies in patients with chronic viral liver disease would be valuable for establishing appropriate vaccination guidelines for patients with chronic liver disease.

### Innovations and breakthroughs

Recent studies reported a rapid epidemiological shift in HAV infection. In this study, the authors evaluated seroprevalence of IgG anti-HAV in patients with chronic liver disease using large population based data, and investigated the age-specific seroprevalence and the factors that affect IgG anti-HAV seropositivity.

### Applications

There has been an apparent epidemiological shift in HAV seroprevalence in patients with chronic liver disease. Most patients who are above 40 years of age have already been exposed to HAV. Therefore, vaccination against HAV should be considered, particularly for young anti-HAV-negative patients with chronic liver disease.

### Peer review

This manuscript is of interest.

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S- Editor Sun H L- Editor Webster JR E- Editor Lin YP