J Korean Med Sci 1998; 13: 306-10
ISSN 1011-8934

Prevalence of Viral Hepatitis Markers in Korean Patients with Hepatocellular Carcinoma

The positive rates of hepatitis B surface antigen (HBsAg) and antibody to hepatitis C virus (anti-HCV) were analyzed according to year, sex, age, and serum ALT levels in 1,370 patients with hepatocellular carcinoma (HCC) who visited the Korea Cancer Center Hospital between January 1989 and December 1994. The positive rate of HBsAg was 68.8 to 76.0% per year in patients with HCC, while that of anti-HCV was 3.2 to 9.8% per year. No sex predominance was found in the positive rates of HBsAg and anti-HCV. HBsAg positivity was distributed mostly in the 41 to 50 age group, whereas anti-HCV positivity was distributed mostly in the over 50 age group. Higher positive rate of anti-HCV was observed in HCC patients with serum ALT levels above the normal range than in those with serum ALT levels within the normal range. However, elevated serum ALT levels above the normal range was not related to the positve rate of HBsAg. The relatively low prevalence of anti-HCV in patients with HCC suggests that the role of HCV infection in the development of HCC lower than that of HBV infection in Korea. However, our results suggest that HCV is another potent risk factor for HCC even in HBV endemic areas.

Key Words : *Carcinoma hepatocellular; Hepatitis B surface antigen; Hepatitis C antibodies*

Kwang Huh, Soo-Yong Choi*, You-Sung Whang†, Dong-Soon Lee

Department of Clinical Pathology and Laboratory of Clinical Research*, Korea Cancer Center Hospital: Blood Research Institute, Central Blood Center, Korean Red Cross†, Seoul, Korea

Received : May 26, 1997
Accepted : March 6, 1998

Address for correspondence
Dong-Soon Lee, M.D., Ph.D.
Department of Clinical Pathology, Korea Cancer Center Hospital, 215-4 Gongrung-dong, Nowon-gu, Seoul 139-706, Korea
Tel : (02) 970-1261, Fax : (02) 978-2005

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers among Koreans. The crude annual incidence rate in Seoul from 1991 to 1992 was reported as 21.1 per 100,000 for males and 7.0 for females (1). The mortality rate of HCC among Koreans was one of the highest in the world and was reported as 35.4 per 100,000 for males and 12.0 for females in 1990 (2). Chronic hepatitis caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) infection has been estimated as a major risk factor for the development of HCC in Koreans (3-5). Previous studies of the prevalence of viral hepatitis markers in Korean patients with HCC showed that only a small proportion of patients (10.3-17.0%) were positive for the antibody to HCV (anti-HCV) and suggested that HCV infection seemed to play a less important role in the etiology of HCC in Korea where HBV is highly endemic compared to HCV infection (3-5). These results are likely to be consistent with the reports of other countries where HBV is endemic, such as China (6, 7), Taiwan (8-10), and South Africa (11). However, the prevalence of anti-HCV positivity varies among the reports of several institutions in Korea; Shin et al. reported 10.3% anti-HCV total positivity based on a study of 194 patients with HCC from August 1990 to February 1993 (4), whereas Lee et al. reported 17.0% anti-HCV total positivity among 336 patients with HCC between November 1990 and May 1991 (5). However, these studies were performed not only with few subjects but also for short periods. In addition, they determined the positivity of anti-HCV using mainly the 1st generation enzyme immunoassay (EIA) test. It seems to be necessary to evaluate prevalence with a more number of subjects and for a longer period, and using the 2nd generation EIA test which is known to show improved sensitivity and specificity compared to the 1st generation EIA test (12, 13). Our studies included more patients with HCC for a longer period than previous studies in Korea. Furthermore, we analyzed the distribution of the seroprevalence of HBsAg and anti-HCV in patients with HCC according to sex, age, and serum ALT levels.

Table 1. The positive rates of HBsAg and anti-HCV in patients with hepatocellular carcinoma (HCC) by year

Year	HBsAg (+)		Anti-HCV (+)		HBsAg (+) & Anti-HCV (+)	
	No. tested	Positive rate (%)	No. tested	Positive rate (%)	No. tested	Positive rate (%)
1989	178	70.8	-	-	-	-
1990	248	73.0	-	-	-	-
1991	208	68.8	127	3.2	120	0
1992	233	72.5	215	9.8	214	1.9
1993	200	76.0	192	8.3	192	1.0
1994	254	74.0	248	6.5	248	1.2
Total	1,321	72.6	782	7.4	774	1.2

MATERIALS AND METHODS

Subjects

The subjects consisted of 1,370 patients with HCC who were admitted to the Korea Cancer Center Hospital between January 1989 and December 1994. Among them, 1,321 patients were tested for HBsAg from January 1989 to December 1994, while 782 patients were tested for anti-HCV from January 1990 to December 1994. The number of cases confirmed by histologic findings, such as aspiration cytology or liver biopsy were 722 cases (52.7%). Without histological confirmation, the diagnosis of HCC was accepted in the 648 cases (47.3%) based on the appropriate radiological findings of the liver, such as ultrasonography, computed tomography, or angiography accompanied with elevated serum alpha-fetoprotein (AFP) levels.

Serologic tests

HBsAg was detected by radioimunoassay (RIA) from January 1989 to December 1990 and thereafter by enzyme immunoassay (EIA) (Abbott Lab., Chicago, IL, U.S.A.). Anti-HCV was detected by the 2nd generation EIA method (Abbott Lab., Chicago, IL, U.S.A.).

Statistical analysis

The chi-square test or Student t-test was used for group comparisons using the SPSS (Statistical Pakages for Social Science) program.

RESULTS

The positive rates of HBsAg and anti-HCV among patients with HCC patients by year

The positive rate of HBsAg among 1,321 patients with HCC from January 1989 to December 1994 was 68.8 to 76.0% per year, while that of anti-HCV among 782 patients with HCC from January 1991 to December 1994 was 3.2 to 9.8%. The rate of coinfection with HBV and HCV in 774 patients with HCC was less than 1.9% per year from January 1991 to December 1994 (Table 1).

The positive rates of HBsAg and anti-HCV according to sex

As shown in Table 2 and 3, the overall prevalence of HBsAg was slightly higher in males (73.7%) than in females (67.6%) in patients with HCC, but the difference was not statistically significant ($P>0.1$). The overall prevalence of anti-HCV did not show preponderance ($P>0.1$) between males (7.1%) and females (7.3%).

The positive rates of HBsAg and anti-HCV according to age

As shown in Tables 2 and 3, the prevalence of HBsAg in patients with HCC was higher in the 41 to 50 age group than in any other age group. On the other hand, the positive rate of anti-HCV in patients with HCC was the highest in the over 51 age group. The positive rate

Table 2. The postive rate of HBsAg in patients with hepatocellular carcinoma (HCC) according to sex and age

Group		No. tested	Positive rates (%)
Sex	Male	1,080	73.7*
	Female	241	67.6
Age (year)	0-20	7	28.6
	21-30	16	81.3
	31-40	123	84.6
	41-50	366	86.0†
	over 51	809	64.9

*$P>0.1$ compared with females
†$P<0.01$ compared with 20 and over 51 age groups

Table 3. The positive rate of anti-HCV in patients with hepatocellular carcinoma (HCC) according to sex and age

Group		No. tested	Positive rates (%)
Sex	Males	631	7.1*
	Females	151	7.3
Age	0-20	3	0
	21-30	10	0
	31-40	84	0
	41-50	218	1.8
	over 51	467	11.1†

*P>0.1 compared with females
†P<0.01 compared with 31-40 and 41-50 age groups

of HBsAg had a tendency to increase from less than 20 age group to 41-50 age group and then declined abruptly from over 51 age group. However, patients with anti-HCV positivity were not found from less than 20 age group to 41-50 age group and increased abruptly from over 51 age group.

The positive rates of HBsAg and anti-HCV according to serum ALT levels

Although the prevalence of HBsAg was slightly higher in HCC patients above the serum ALT level 30 IU/L (76.7%) than in those with below this ALT level (64.7 %), these figures were not statistically significant (P> 0.1). On the other hand, the prevalence of anti-HCV was significantly higher (P<0.05) in HCC patients above the serum ALT level 30 IU/L (8.2%) than in those with below this ALT level (5.2%) (Table 4).

Table 4. The positive rates of HBsAg and anti-HCV in patients with hepatocellular carcinoma (HCC) according to serum ALT levels

Group		No. tested	Positive rates (%)
HBsAg (+)	ALT*< 30	453	64.7
	ALT > 30	868	76.7†
Anti-HCV (+)	ALT < 30	271	5.2
	ALT > 30	511	8.2‡

*Unit: IU/L
†P>0.1 compared with ALT<30
‡P<0.05 compared with ALT<30

DISCUSSION

The incidence of HCC is particularly high in Southeastern Asia and Africa in geographical distribution (15, 16). In these areas, several countries, such as China (6, 7), Taiwan (8-10), Hong Kong (17), Korea (3-5), Mozambique (18), and South Africa (11) have been known as HBV endemic areas. HBV infection has long been considered as a major risk factor for the development of HCC, particularly where HBV is endemic (19). However, since the discovery of HCV (20) and the development of the EIA test which can detect anti-HCV (21), many studies concerning the association of both HBV and HCV infections with HCC have been performed by many researchers from different countries. These studies have been reported that HCV infection is another major pathogenic agent that could independently contribute to the development of HCC and that the prevalence of HCV infection estimated as anti-HCV positivity varies depending on its geographical distribution (22). In Japan where the incidence of HCC is one of the highest in the world, the prevalence of anti-HCV reported was also the highest among Far Eastern countries (23, 24). Hamasaki et al. reported that the positive rate of anti-HCV was 58% in HBsAg negative patients with HCC (24). This result was as high as the prevalence in Western countries (54.0-55.5%), such as Spain (25) and Italy (26). On the other hand, the reports from southern China (7), Taiwan (8-10), Hong Kong (17), and Korea (4, 5) showed a relatively low prevalence of anti-HCV positivity in patients with HCC. In Taiwan (8-10), anti-HCV positivity was reported to be from 11.0 to 19.5%, whereas in Hong Kong (17) and the Guangxi province of southern China (7) the prevalence of anti-HCV was reported to be 7.3 and 5.4%, respectively.

Even in Korea, reports regarding the prevalence of anti-HCV in patients with HCC varied from one institution to another. Shin et al. reported that the positive rate of anti-HCV in 184 patients with HCC was 10.3% (4), while Lee et al. reported 17.0% of anti-HCV positivity in 336 patients with HCC (6). Our results of the positive rate of anti-HCV were lower than these two studies in Korean patients with HCC and rather comparable to those of Hong Kong (17) and the Guangxi province of southern China (7). This variability of the prevalence of anti-HCV even in Korea may be attributed, in part, to the methods of anti-HCV EIA tests used in these studies. Since the 1st generation EIA test which detects anti-c100-3 was found to produce false positive results particularly when old sera were used (27), the previous studies by Shin et al. and Lee et al. which used mainly the 1st generation EIA test might be considered an overestimation of anti-HCV positivity compared with our studies which used the 2nd generation EIA test which detects anti-c22-3 and anti-c33c as well as anti-c100-3. A lower prevalence of anti-HCV reported in the Guangxi province of southern China (7) in which the 2nd

generation EIA test was used, unlike other reports from Taiwan (8-10) and Hong Kong (17) where the 1st generation EIA test was used, seems to support our results on anti-HCV positivity. However, since previous reports based on the 2nd generation EIA test have been considerably rare so far, further studies not only with 2nd generation EIA test but also with 3rd generation EIA test will be required to clarify the variability of the prevalence of anti-HCV caused by the different methods of EIA tests. On the assumption that confounding risk factors for HCC other than viral factor are almost identical in Korea, the characteristics of the study population and the duration of study may be the other possible explanations for the variability of anti-HCV positivity.

While Jung et al. reported a decreasing tendency in the annual trend of both HBsAg (from 6.87% to 3.76% per year) and anti-HCV positivities (from 0.58% to 0.37 % per year) in blood donors (14), no such tendency was demonstrated in patients with HCC. However, it is still unclear whether the decreasing tendency of these viral hepatitis markers in blood donors reflects the actual reduction of viral hepatitis infection in the general population or the improved specificity of the EIA test (14).

With respect to age distribution, our results tend to be comparable to the previous study by Lee et al. (6) in Korea in which they reported that the mean age was 51.6 for HBsAg positive patients and 60.4 for anti-HCV positive patients with HCC. Our results showed approximately 10 years difference in age distribution in the prevalence of HBsAg beween HCC patients (subjects aged 41 to 50 had the highest positive rate) and healthy blood donors (subjects aged 31 to 40 had the highest positive rate), but no difference in age distribution in the prevalence of anti-HCV between patients with HCC and blood donors (subjects aged over 51 had the highest positive rate) (14). This seems to support the idea that even though HCC usually develops only after 20 to 30 years of HBV infection (19) and about 30 years of HCV infection (28), hepatocarcinogenesis proceeds rapidly particularly in elderly patients with HCV infection in Korea and Japan (5, 28).

No overall predominance of sexes in the prevalence of HBsAg and anti-HCV was observed in our study. This may be inconsistent with the previous reports which suggested that the male gender was associated not only with a higher incidence of HCC (29) but also with a higher prevalence of HBV or HCV infection (30, 31). However, previous reports with regard to the epidemiologic studies of the prevalence of viral hepatitis markers particularly in patients with HCC did not pay much attention to the sex distribution of viral hepatitis markers and smaller female population was included in these studies. Even though Jung et al. reported that the prevalences of HBsAg (males: 3.90-7.29%, females: 2.71-4.41% per year) and anti-HCV (males: 0.37-0.59%, females: 0.31-0.42% per year) were higher in male blood donors than in females (14), the predominance of sexes in HCC patient with HBsAg or anti-HCV positivity cannot be proved statistically in our study.

A higher prevalence of anti-HCV was observed in HCC patients with serum ALT levels above the normal range than in those with serum ALT levels within the normal range. This suggest a relationship between raised ALT levels above the normal range and the positivity of anti-HCV for HCC patients, which is similar to the reports by Jung et al. (14) and Kim et al. (30). However, there was no relationship between the elevated serum ALT levels and the prevalenc of HBsAg, which is inconsistent with the reports by Jung et al. (14).

In conclusion, despite the fact that the prevalence of HCV is lower than that of HBV in Korean patients with HCC, HCV infection alone may play a potent and independent role in hepatocarcinogenesis, particularly in elderly patients. Since variability in the prevalence of anti-HCV might be originated from the differeces in the test methods and the characteristics of the study population such as distribution of age and sex of study population, further studies with more subjects, particularly females, for longer periods, and 3rd generation EIA method appear to be necessary to clarify the proportion of the HCV infection in patients with HCC. The interaction between HBV and HCV infection in increasing risk of hepatocarcinogenesis need to be studied by carrying out case-control study using epidemiologically comparable control group.

REFERENCES

1. Kim JP, Park IS, Ahn YO, Shin MH, Ahn DH, Kang TW, Ko UR, Ku PS, Kim KY, Kim KH, Kim NK, Kim DJ, Kim DH, Kim BS, Kim SH, Park CT, Min JS, Park TK, Woo BH, Yoo H, Lee SW, Lee SJ, Cho KS, Joo HZ, Ham EK. *1991 Cancer incidences in Seoul, Korea: Results of the implementation study of Seoul cancer registry. J Korean Med Sci 1995; 10: 74-84.*
2. National Bureau of Statistics. *Annual report on the cause of death statistics 1990, Korea, 1991.*
3. Kim KH, Lee HR, Min CH, Jeong H, Hong SH, Lee YS, Cha YJ, Yoo BC, Park SM. *Prevalence of antibodies to hepatitis C virus in patients with various types of liver diseases. Korean J Intern Med 1992; 7: 9-11.*
4. Shin HR, Lee CU, Park HJ, Seol SY, Chung MJ, Choi CH. *Risk factors for hepatocellular carcinoma among Koreans - a case-control study in Pusan, Korea. In: Summary Report, Japan-Korea joint study on liver cancer. Fukuoka University, School*

of Medicine, 1993.

5. Lee HS, Han CJ, Kim CY. *Predominant etiologic association of hepatitis C virus with hepatocellular carcinoma compared with hepatitis B virus in elderly patients in a hepatitis B-endemic area. Cancer 1993; 72: 2564-7.*
6. Beasley RP. *Hepatitis B virus: the major etiology of hepatocellular carcinoma. Cancer 1988; 61: 1942-56.*
7. Okuno H, Xie ZC, Lu BY, Qin X, Takasu M, Kano H, Shiozaki Y, Inoue K. *A low prevalence of anti-hepatitis C virus antibody in patients with hepatocellular carcinoma in Guangxi province, southern China. Cancer 1994; 73: 58-62.*
8. Yu MW, You SL, Chang AS, Lu SN, Chen CJ. *Association between hepatitis C virus antibodies and hepatocellular carcinoma in Taiwan. Cancer Res 1991; 51: 5261-5.*
9. Lee SD, Lee FY, Wu JC, Hwang SJ, Wang SS, Lo KJ. *The prevalence of anti-hepatitis C virus among Chinese patients with hepatocellular carcinoma. Cancer 1992; 69: 342-5.*
10. Chung WL, Chang WY, Lu SN, Su WP, Lin ZY, Chen SC, Hsieh MY, Wang LY, You SL, Chen CJ. *The role of hepatitis B and C virus in hepatocellular carcinoma in hepatitis B endemic area: a case-control study. Cancer 1992; 69: 2052-4.*
11. Kew MC, Houghton M, Choo QL, Kuo G. *Hepatitis C virus antibodies in southern African blacks with hepatocellular carcinoma. Lancet 1990; 335: 873-4.*
12. Nakatsuji Y, Matsumoto A, Tanaka E, Ogata H, Kiyosawa K. *Detection of chronic hepatitis C virus infection by four diagnostic system: first-generation and second-generation enzyme-linked immunosorbent assay, second-generation recombinant immunoblot assay and nested polymerase chain reaction analysis. Hepatology 1992; 16: 300-5.*
13. Yatsuhashi H, Inoue O, Koga M, Nagayaki S, Mizuno K, Kolberg J, Beall E, Cha TA, Irvine B, Kuo G, Ureda MS, Yano M. *Comparision of hepatitis C markers in patients with NANB hepatitis. J virol Methods 1992; 37: 13-22.*
14. Jung BC, Lee SH, Kim SI. *Prevalence of HBsAg and anti-HCV among Korean blood donors. Korean J Blood Transfusion 1994; 5: 143-50.*
15. Szmuness W. *Hepatocellular carcinoma and the hepatitis B virus: evidence for a causal association. Prog Med Virol 1978; 24: 40-69.*
16. Beasley RP, Hwang LY, Lin CC, Chen CS. *Hepatocellular carcinoma and hepatitis B virus; a prospective study of 22,707 men in Taiwan. Lancet 1981; 2: 1229-33.*
17. Leung NW, Tam JS, Lai JY, Leung TW, Lau WY, Shiu W, Li AK. *Does hepatitis C virus infection contribute to hepatocellular carcinoma in Hong Kong? Cancer 1992; 70: 40-4.*
18. Dazza MC, Meneseses LV, Giard PM, Villaroel C, Brechlot C, Larouze B. *Hepatitis C virus antibody and hepatocellualr carcinoma. Lancet 1990; 335: 1216.*
19. Milich DR, Jones J, Hughes J, Maruyama T. *Hepatitis B virus infection, the immune response and hepatocellular carcinoma. Ciba Found Symp 1994; 187: 113-29.*
20. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradly DW, Houghton M. *Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989; 244: 352-62.*
21. Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, Miyamura T, Dienstag JL, Alter MJ, Stevens CE, Tegtmeier GE, Bonino F, Colombo M, Lee WS, Kuo C, Berger K, Shuster JR, Overby LR, Bradley DW, Houghton M. *An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. Science 1989; 244: 362-4.*
22. Resnick RH, Koff R. *Hepatitis C-related hepatocellular carcinoma, prevalence and significance. Arch Intern Med 1993; 153: 1672-7.*
23. Nishioka K, Watanabe J, Furuta S, Tanaka E, Iino S, Suzuki H, Tsuji T, Yano M, Kuo G, Choo QL, Houghton M, Oda T. *A high prevalence of antibody to the hepatitis C virus in patients with hepatocellular carcinoma in Japan. Cancer 1991; 67: 429-33.*
24. Hamasaki K, Nakata K, Tsutsumi T, Tsuruta S, Nakao K, Kato Y, Shima M, Koji T, Nagataki S. *Changes in the prevalence of hepatitis B and C infection in patients with hepatocellualr carcinoma in the Nagasaki Prefecture, Japan. J Med Virol 1993; 40: 146-9.*
25. Bruix J, Barrera JM, Calvet X, Ercilla G, Costa J, Sanchez-Tapias JM, Ventura M, Vall M, Bruguera M, Bru C, Castillo R, Rodes J. *Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. Lancet 1989; 2: 1004-6.*
26. Colombo M, Kuo G, Choo QL, Donato MF, Del Ninno E, Tommasini MA, Dioguardi N, Houghton M. *Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellualr carcinoma. Lancet 1989; 2: 1006-8.*
27. Lok AS, Ma OC, Chen TM, Lai CL, Chung HT, Ng CP, Lam JS. *Overestimation of the prevalence of antibody to hepatitis C virus in retrospective studies on stored sera. Hepatology 1991; 14: 752-62.*
28. Yano M, Yatsuhashi H, Inoue O, Inokuchi K, Koga M. *Epidemiology and long term prognosis of hepatitis C virus infection in Japan. Gut 1993; suppl: 13-6.*
29. Kew MC. *The development of hepatocellular cancer in humans. Cancer Surv 1986; 5: 719-39.*
30. Kim YS, Pai CH, Chi HS, Kim DW, Min YI, Ahn YO. *Prevalence of hepatitis C virus antibody among Korean adults. J Korean Med Sci 1992; 7: 333-6.*
31. Tassopoulos NC, Hatzakis A, Delladetsima I, Koutelou MG, Todoulos A, Miriagou V. *Role of hepatitis C virus in acute non-A, non-B hepatitis in Greece: a 5-year prospective study. Gastroenterology 1992; 102: 969-72.*