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ORIGINAL ARTICLE

Positive Rate of Different Hepatitis B Virus Serological Markers in Peking Union Medical College Hospital, a General Tertiary Hospital in Beijing[△]

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Objectives To investigate the positive rate of different hepatitis B virus (HBV) serological markers, and the demographic factors related to HBV infection.

Methods We enrolled all patients tested for HBV serological markers, such as HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), HBV core antibody (HBcAb), and HBV-DNA from July 2008 to July 2009 in Peking Union Medical College Hospital. The positive rate of each HBV serological marker was calculated according to gender, age, and department, respectively. The positive rates of HBV-DNA among patients with positive HBsAg were also analyzed.

Results Among 27 409 samples included, 2681 (9.8%) were HBsAg positive. When patients were divided into 9 age groups, the age-specific positive rate of HBsAg was 1.2%, 9.6%, 12.3%, 10.9%, 10.3%, 9.7%, 8.0%, 5.8%, and 4.3%, respectively. The positive rate of HBsAg in non-surgical department, surgical department, and health examination center was 16.2%, 5.8%, and 4.7%, respectively. The positive rate of HBsAg of males (13.3%) was higher than that of females (7.3%, $P=0.000$). Among the 2681 HBsAg (+) patients, 1230 (45.9%) had HBV-DNA test, of whom 564 (45.9%) were positive. Patients with HBsAg (+), HBeAg (+), and HBcAg (+) result usually had high positive rate of HBV-DNA results (71.8%, $P=0.000$).

Conclusions Among this group of patients in our hospital, the positive rate of HBsAg was relatively high. Age group of 20-29, males, and patients in non-surgical departments were factors associated with high positive rate of HBsAg.

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CHINA is one of the countries that have the most carriers of hepatitis B virus (HBV), accounting for nearly 10% of the world. The disease burden of HBV infection and associated hepatocellular carcinoma (HCC) in China is also believed to be the heaviest in the world.¹ According to the results of the national HBV epidemiological investigation in 2006,² 7.18% of Chinese people between 1 and 59 years old have positive HBV surface antigen (HBsAg). According to this, there are about 93 000 000 people with HBV infection now in China, of whom 20 000 000 people have chronic hepatitis B. But as it has been years from now, we may need new epidemiological investigation to get new data. However, there are limited data on HBV infection rate and viral load of patients in general tertiary hospitals in China. So we retrospectively investigated the positive rate of HBV serological markers of patients in Peking Union Medical College Hospital (PUMCH) from July 2008 to July 2009, and analyzed the demographic factors related to the prevalence of HBV infection in order to provide evidence for formulating preventive measures against nosocomial transmission.

PATIENTS AND METHODS

Data collection

We retrospectively enrolled all patients who were tested for HBV serological markers, such as HBsAg, HBV surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), and HBV core antibody (HBcAb) in the Center Clinical Laboratory and Department of Infectious Disease in PUMCH from July 2008 to July 2009. We collected demographic information including age, gender, departments, and dates of testing from laboratory records. For HBsAg-positive patients, the results of HBV-DNA were sought based on patients' unique hospital record number, and collected if available.

Laboratory examination

Hepatitis B virus serological markers were examined by Abbott i2000 Automatic chemiluminescence immune analyzer (Abbott Laboratories, Chicago, USA). HBV-DNAs were examined using polymerase chain reaction (PCR) fluorescent probe method on the ABI Prism5700 (Zhongshan University Da'an Gene Limited Liability Company, Guangzhou, China).

Study design

All patients were divided into 9 groups that were 0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and ≥ 80 age group, the positive rates of HBsAg, HBsAb, HBeAg, HBeAb,

and HBcAb were calculated in each group. They were also divided into 3 groups in which the patients were from non-surgical department (outpatient and inpatient), surgical department (outpatient and inpatient), and health examination center respectively, and the positive rates of HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb were calculated respectively. The testing rate and positive rate of HBV-DNA were calculated among HBsAg positive patients.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables of normal distribution were expressed as means $\pm$ standard deviation (SD). Continuous variables of non-normal distribution were expressed as median and interquartile range (IQR). Categorical data were expressed as percentages. The Pearson's Chi-square test was used to compare the proportions between groups of males and females, and of surgical department and non-surgical department; and among different age groups, among surgical department, non-surgical department, and health examination center. $P < 0.05$ was considered statistically significant.

RESULTS

General conditions

A total of 27 409 patients were enrolled in this study. Among these patients, 13 952 (50.9%) were from outpatient, 11 659 (42.5%) were from inpatient, and 1798 (6.6%) were from health examination center.

Results of different genders

Males had a higher positive rate of HBsAg than females. The proportions of patients with HBsAg (+), HBeAg (+), HBcAb (+) results and HBsAg (+), HBeAb (+), HBcAb (+) results were also higher among males than those among females. The differences were statistically significant ($P < 0.01$, Table 1).

Results of different age groups

The differences among age-groups were statistically significant (all $P < 0.01$). The positive rate of HBsAg was the lowest in the age group of 0-9 (1.2%), and the highest in the age group of 20-29 (12.3%). The positive rate of HBsAg, HBeAg and HBcAb was the lowest in the age group of over 80 years old (0.3%), and the highest in the age group of 10-19 (6.8%). The positive rate of HBsAg, HBeAb and HBcAb was the lowest in the age group of 0-9 (0.6%), and the highest in the age group of 40-49 (7.6%). (Table 2)

Table 1. Comparisons of positive rate of the HBV serological markers of patients of different genders

Gender	Case number	HBsAg (+)		HBsAg, HBeAg, HBcAb (+)		HBsAg, HBeAb, HBcAb (+)		HBsAb, HBcAb (+)	
		Case number	Positive rate (%)	Case number	Positive rate (%)	Case number	Positive rate (%)	Case number	Positive rate (%)
Male	11 206	1496	13.3	443	4.0	979	8.7	3121	27.9
Female	16 203	1185	7.3	283	1.7	819	5.1	3963	24.5
P value		0.000		0.000		0.000		0.000	
Gender	Case number	HBcAb (+)		HBsAb (+)		All (-)			
		Case number	Positive rate (%)	Case number	Positive rate (%)	Case number	Positive rate (%)	Case number	Positive rate (%)
Male	11 206	5557	49.6	5142	45.9	3650	32.6		
Female	16 203	6053	37.4	7942	49.0	6174	38.1		
P value		0.000		0.000		0.000		0.000	

HBV: hepatitis B virus; HBsAg: HBV surface antigen; HBsAb: HBV surface antibody; HBeAg: hepatitis B e antigen; HBeAb: hepatitis B e antibody; HBcAb: HBV core antibody.

Table 2. Comparisons of positive rate of the HBV serological markers of patients among different age groups

Age (yrs)	Case number	HBsAg (+)		HBsAg, HBeAg, HBcAb (+)		HBsAg, HBeAb, HBcAb (+)		HBsAb, HBcAb (+)	
		Case number	Positive rate (%)	Case number	Positive rate (%)	Case number	Positive rate (%)	Case number	Positive rate (%)
0-9	329	4	1.2	2	0.6	2	0.6	18	5.5
10-19	1139	109	9.6	78	6.8	25	2.2	86	7.6
20-29	3733	459	12.3	185	5.0	250	6.7	641	17.2
30-39	6170	672	10.9	196	3.2	426	6.9	1543	25.0
40-49	5653	584	10.3	127	2.2	430	7.6	1550	27.4
50-59	4855	470	9.7	88	1.8	358	7.4	1417	29.2
60-69	3097	247	8.0	35	1.1	199	6.4	999	32.3
70-79	2065	120	5.8	14	0.7	97	4.7	693	33.6
≥80	368	16	4.3	1	0.3	11	3.0	137	37.2
Total	27 409	2681	9.8	726	2.6	1798	6.6	7084	25.8
P value		0.000		0.000		0.000		0.000	
Age (yrs)	Case number	HBcAb (+)		HBsAb (+)		All (-)			
		Case number	Positive rate (%)	Case number	Positive rate (%)	Case number	Positive rate (%)	Case number	Positive rate (%)
0-9	329	27	8.2	200	60.8	120	36.5		
10-19	1139	203	17.8	621	54.5	403	35.4		
20-29	3733	1176	31.5	2100	56.3	1096	29.4		
30-39	6170	2434	39.4	3093	50.1	2183	35.4		
40-49	5653	2463	43.6	2558	45.3	2184	38.6		
50-59	4855	2303	47.4	2109	43.4	1876	38.6		
60-69	3097	1623	52.4	1331	43.0	1147	37.0		
70-79	2065	1165	56.4	897	43.4	699	33.8		
≥80	368	216	58.7	175	47.6	116	31.5		
Total	27 409	11 610	42.4	13 084	47.7	9824	35.8		
P value		0.000		0.000		0.000		0.000	

Results of different departments

The positive rate of HBsAg of patients in outpatient departments was higher than that in inpatient departments (13.7% vs. 5.9%, $P < 0.01$). We also observed that the

positive rate of HBsAg of patients from non-surgical departments was higher than those from surgical departments. The differences between outpatients and inpatients of non-surgical department were statistically significant, and

differences among non-surgical departments, surgical departments, and health examination center were also statistically significant (all $P<0.01$). (Table 3)

Results of HBV-DNA tests

Among the 2681 patients with positive HBsAg, 1230 (45.9%) examined HBV-DNA, and among these patients who examined HBV-DNA, 564 (45.9%) were positive, with a median HBV-DNA level of 3.0×10^5 copies/ml (IQR $1.7\times$

10^4 - 1.3×10^7). Among the 726 patients with HBsAg (+), HBeAg (+) and HBcAb (+) results, 347 (47.8%) examined HBV-DNA, and 249 (71.8%) had positive results, with a median HBV-DNA level of 3.6×10^6 copies/ml (IQR 8.6×10^4 - 4.6×10^7). Among the 1798 patients with HBsAg (+), HBeAb (+) and HBcAb (+) results, 562 (31.3%) examined HBV-DNA, 179 (31.9%) had positive results, with a median HBV-DNA level of 3.0×10^4 copies/ml (IQR 7.3×10^3 - 2.1×10^5) ($P=0.000$).

Table 3. Comparisons of positive rate of the HBV serological markers of patients among different departments

Department	Case number	HBsAg (+)		HBsAg, HBeAg, HBcAb (+)		HBsAg, HBeAb, HBcAb (+)		HBsAb, HBcAb (+)	
		Case number	Positive rate (%)	Case number	Positive rate (%)	Case number	Positive rate (%)	Case number	Positive rate (%)
Non-surgical department	10 571	1717	16.2	535	5.1	1078	10.2	2693	25.5
Outpatient	6663	1482	22.2	485	7.3	905	13.6	1621	24.3
Inpatient	3908	235	6.0	50	1.3	173	4.4	1072	27.4
P value			0.000		0.000		0.000		0.000
Surgical department	15 040	879	5.8	175	1.2	652	4.3	3794	25.2
Outpatient	7289	423	5.8	80	1.1	310	4.3	1728	23.7
Inpatient	7751	456	5.9	95	1.2	342	4.4	2066	26.7
P value			0.835		0.464		0.632		0.000
Health examination center	1798	85	4.7	16	0.9	68	3.8	597	33.2
P value ^a			0.001		0.001		0.001		0.001

Department	Case number	HBcAb (+)		HBsAb (+)		All (-)	
		Case number	Positive rate (%)	Case number	Positive rate (%)	Case number	Positive rate (%)
Non-surgical department	10 571	5214	49.3	4603	43.5	3469	32.8
Outpatient	6663	3568	53.5	2779	41.7	1956	29.4
Inpatient	3908	1646	42.1	1824	46.7	1513	38.7
P value			0.000		0.000		0.000
Surgical department	15 040	5594	37.2	7457	49.6	5785	38.5
Outpatient	7289	2487	34.1	3826	52.5	2700	37.0
Inpatient	7751	3107	40.1	3631	46.8	3085	39.8
P value			0.000		0.000		0.001
Health examination center	1798	802	44.6	1024	57.0	570	31.7
P value ^a			0.001		0.001		0.001

a: comparisons among groups of non-surgical department, surgical department, and health examination center.

DISCUSSION

After the launch of national programmed immunization of hepatitis B, the prevalence of HBV infection is declining, especially in young children. However, HBV infection remains

a major public health challenge and a heavy disease burden in China.² With successful blockage of vertical transmission of HBV by vaccine and immunoglobulin, it becomes more important to prevent HBV transmission in health-care facilities. Therefore, it will be helpful to have a better knowledge of HBV infection status in patients in

hospitals. PUMCH is one of leading tertiary hospitals that offer comprehensive medical services. It serves more than 3 million outpatients and about 60 000 inpatients every year. So we investigated the positive rate of HBV serological markers and HBV-DNA of patients in PUMCH. And as the diagnostic and treatment guideline for chronic hepatitis B enacted in 2010 recommended using antiviral drugs, the positive rate of HBV serological markers might be affected by the anti-HBV drugs after 2010, so we analyzed the data of one year between 2008 and 2009.

In our study, age group of 0-9 had the lowest HBsAg positive rate (1.2%), the age group of 20-29 had the highest positive rate of HBsAg (12.3%), and the positive rate of HBsAg declined among patients who were 60 years old and older. This was the same as the result of investigation of viral hepatitis performed in 6 regions of China,² probably due to deaths caused by HBV-related cirrhosis and HCC in patients over 60 years old.³ HCC is the fifth most common death of tumors of males, and the seventh of females, accounting for 7% of all the cancers in China. The most important risk factor of HCC is cirrhosis, while cirrhosis is mainly caused by HBV or hepatitis C virus.¹ It is estimated that 25%-40% of HBV carriers who are infected with the virus early in their lives will eventually develop into disastrous complications such as liver cirrhosis, hepatic decompensation, and HCC.⁴ So preventing HBV infection is important. As the backbone of preventing HBV infection is HBV vaccination, all the newborns and people who have high risk of HBV infection such as health workers are recommended to be vaccinated.⁵ Thanks to the world's HBV vaccine program, prevalence and incidence of HBV has decreased in many countries.⁶ After vaccination, new HBV infection and prevalence of HCC greatly decreased in Eastern Asia and South Africa as reported.⁷ In our study, positive rate of HBsAg was the lowest in the age group of 0-9, and positive rate of HBsAb was the highest in this group, which was in line with results of other viral hepatitis epidemic investigations.² These indicated the strong protective effects of the HBV vaccination introduced in 1992 and integrated into the national immunization program in 2002.

As being reported by Baig,⁸ the positive rate of HBsAg was higher in males than that in females, and we observed the same result. It had been suggested that estrogen might play an important role in protecting hepatic cells from developing to chronic liver disease.⁸ Our study showed 9.8% of patients were HBsAg positive, which was higher than the results of the national HBV epidemiology investigation in 2006.² According to that investigation, 7.18% of the 1-59 years old people in China were HBsAg positive. The reason

might be that the age distribution and the general health condition of patients in our hospital were different from general population, and patients from hepatitis clinic with high positive rate of HBsAg were included. This also explained why the positive rate of HBsAg in patients of non-surgical departments was higher than that of surgical departments (16.2% vs. 5.8%), and higher of outpatient departments than that of inpatient departments, which might also be the reason of high variation of HBsAg prevalence among individuals from non-surgical department, surgical department, and health examination. As the data were from a single centre, the results might have some bias.

HBsAg, HBeAg and HBcAg positive patients had the highest testing rate of HBV-DNA (47.8%), and positive rate of HBV-DNA was the highest (71.8%). HBsAg, HBeAb and HBcAb positive patients had a relative lower positive rate of HBV-DNA (31.9%), which might because those patients had already experienced serological conversion, and the risk of transmission was relatively low. However, 31.9% of HBeAg negative patients had positive HBV-DNA results, which suggested that some of HBeAg negative patients also had high viral load and infectivity. This might be associated with mutation of pre-C and C region's promoter of HBV double strand.⁹ Healthcare workers should pay attention to the potential risk of HBV transmission from HBeAg negative patients.

In the initial 2-3 decades of life, HBV infection is characterized by an immune tolerance phase with positive HBeAg, high serum HBV viral load, normal ALT levels and minimal histological damage.¹⁰ This is followed by an immune-clearance phase, which may lead to HBeAg seroconversion. Based on the results of cross-sectional studies, serum HBsAg levels were generally higher in the immune tolerant patients than those in the ones with immune-clearance.^{4, 11-14} HBsAg levels are higher in HBeAg-positive patients than those in HBeAg-negative patients.¹¹⁻¹³

A retrospective cohort analysis of 360 Taiwanese HBeAg negative patients suggested that when HBV-DNA was higher than 2000 IU/ml, the risk of HBeAg negative hepatitis was increasing, while in low viral load patients (HBV-DNA < 2000 IU/ml), HBsAg could better predict the activation risk of HBeAg negative hepatitis.¹⁵ Groups such as health-care workers, especially surgeons, nurses, and dentists, policemen, barbers, and drivers, are at higher risk of HBV infection.¹⁶ Therefore, whether HBeAg is positive or not, all HBsAg positive patients should have HBV-DNA examination, to confirm whether they have infectivity, and provide evidence for evaluating risk of occupational exposure.

There are some limitations in this study. With retrospective analysis, we were unable to obtain additional

information to further reduce confounding bias or evaluate selection bias. All samples are from a single center, which is the national diagnostic and treatment center of difficult and severe diseases, so our findings may not be representative for other people. And the results may need to be verified in future studies.

In conclusion, among this group of patients in PUMCH, the positive rate of HBsAg was relatively high, especially those of 20-29 age group, males and patients in non-surgical departments. HBeAg negative patients might also have a high viral load. Health workers should pay attention to HBsAg positive patients, and perform HBV-DNA examination to see viral load. Robust measures for prevention should be in place if necessary.

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