

Immune Response to Hepatitis B Vaccination and Factors Associated with Poor Immune Response Among Healthcare Workers

BS Kwan, SG Shim, DH Cho, KM Kim, IS Choi, DG Lee

Department of Medicine,
Samsung Changwon
Hospital, Sungkyunkwan
University School of
Medicine, Changwon, South
Korea

Received:
04-Apr-2019;
Revision:
17-May-2020;
Accepted:
07-Sep-2020;
Published:
12-Jun-2021

ABSTRACT

Background: Hepatitis B virus (HBV) infection is a major global health problem, and healthcare workers (HCWs) are at high risk for HBV infection. Current guidelines strongly recommend immunization and screening for high-risk groups. **Aims:** We evaluated immunization and screening for HBV vaccination, assessed post-vaccination immune status of HCWs and characterized potential risk factors associated with poor immune response. **Materials and Methods:** From January 2010 to December 2018, we retrospectively analyzed comprehensive health checkup data for a total of 303 HCWs who received an HBV vaccination. After vaccination, HBV surface antibody (anti-HBs) titers were collected and the distribution of immune response types was determined. Risk factors for poor immune responses were identified using logistic regression. **Results:** A total of 213 HCWs were analyzed after exclusion based on the exclusion criteria. In total, 28 (13.2%) HCWs had anti-HBs titers <100 mIU/mL (hypo-responsive/nonresponsive groups), and 185 (86.8%) had anti-HBs titers ≥100 mIU/mL (hyper-responsive group). Follow-up observations found that 75% (21/28) of the hypo-responsive/nonresponsive groups did not have increased anti-HBs titers or did not maintain an increased response. A multivariate analysis showed that HBV antibody titers at the time of employment were a significant risk factor (OR, 6.12; CI, 1.34-27.93; $P = 0.019$). **Conclusions:** More attention should be paid to groups that are hypo-responsive/nonresponsive after vaccination and to those with low anti-HBs titers at the beginning of employment. HCWs can be further protected from HBV if their results are discussed at postvaccination follow-ups.

KEYWORDS: Hepatitis B, Vaccination, Healthcare workers, Immune response

INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health problem that is associated with chronic liver disease, cirrhosis, and hepatocellular carcinoma. Approximately 2 billion people are infected around the world, 240 million people are chronic HBV carriers, and approximately 800,000 people die from liver cancer and cirrhosis each year.^[1] In Korea, the majority of chronic HBV infections in children are caused by vertical infection; however, adults, especially healthcare workers (HCWs), are often infected through exposure to blood or body fluids.^[2,3] According to the World Health Organization (WHO), approximately 5.6% of HCWs worldwide are infected with HBV, and approximately

62,000 HBV infections are associated with blood-borne transmission.^[4]

Although there has been a dramatic improvement in antiviral therapy for HBV, only a subset of patients has a sustained response to treatment. Thus, primary prevention of HBV infection by vaccination is known to be an effective preventive measure to reduce the

Address for correspondence: Prof. SG Shim,

Department of Medicine, Samsung Changwon Hospital,
Sungkyunkwan University School of Medicine, 158 Paryong-ro,
Masanhoewongu, Changwon-si, Gyeongsangnam-do, 51353,
South Korea.

E-mail: sgshim218@naver.com

Access this article online

Quick Response Code:



Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_187_19

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Kwan BS, Shim SG, Cho DH, Kim KM, Choi IS, Lee DG. Immune response to hepatitis B vaccination and factors associated with poor immune response among healthcare workers. *Niger J Clin Pract* 2021;24:795-801.

incidence of HBV infection and chronic liver disease and to reduce the number of chronic carriers.^[5-7] HCWs are a high-risk group for HBV infection because of their frequent occupational exposure. Therefore, the American Association For The Study Of Liver Disease (AASLD) 2018 Guidelines strongly recommend immunization and screening for this high-risk group.^[8-10] Generally, a fully immunized individual does not need a booster vaccination, but some patients do not respond to the standard 3-dose HBV vaccine inoculation.^[11,12] Hence, individuals at high risk, such as HCWs, represent groups for which postvaccination evaluations and periodic monitoring of HBV surface antibody (anti-HBs) development are recommended.^[13] Following the recommendations of the WHO, anti-HBs titers are usually measured 6-8 weeks after the completion of three vaccinations to measure the immune response. Levels of measured anti-HBs titers ≥ 10 mIU/mL are generally considered to be protective.^[14]

In Korea, the Korea Centers for Disease Control and Prevention guidelines recommend that HCWs be vaccinated; however, if the administered anti-HBs test is negative, it is recommended to revaccinate these individuals, but there are no detailed recommendations for anti-HBs follow-up tests. For that reason, there is a lack of research on the acquisition of HBV immunity in HCWs in Korea. Thus, this study aimed to assess the postvaccination immune status of HCWs and to characterize potential risk factors associated with a poor immune response.

METHOD AND MATERIALS

Study design and settings

This study is a retrospective observational study conducted from January 2010 to December 2018 at the Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea with HCWs who received the HBV vaccination in an employee comprehensive health checkup. Employee comprehensive health checkups are carried out at the hospital every year, and the HBV vaccination was administered when anti-HBs levels were < 10 mIU/mL. To confirm the vaccine-induced immune response after the vaccination, we conducted anti-HBs testing during the next comprehensive employee screening. The data used in this study are comprehensive screening data that measure HBV antibodies at one-year intervals. We observed changes in antibody levels after the initial antibody immune response. After inoculation, changes in anti-HBs levels were analyzed by dividing HCWs into nonresponsive (anti-HBs titers < 10 mIU/mL), hyporesponsive (anti-HBs titers of 10-100 mIU/mL),

and hyperresponsive (anti-HBs titers ≥ 100 mIU/mL) groups. When additional inoculations were carried out, changes in the anti-HBs titers were also observed after the additional inoculation. The change or persistence of the antibodies after inoculation over the observation period was examined. Since the need for revaccination was high in the hyporesponsive group, the factors associated with the nonresponsive and hyporesponsive groups were analyzed and compared to those associated with the hyperresponsive group.

Sample collection and vaccination schedule

The following data were collected from each subject before vaccination: age at vaccination, sex, weight, height, waist circumference, and body mass index (BMI).

Blood samples were obtained for the anti-HBs titers and liver function blood tests before vaccination. Liver function blood tests included aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ -glutamyl transpeptidase (GGT), albumin, total bilirubin, and direct bilirubin. Fatty liver, a variable factor, was judged to be positive when the calculated fatty liver index (FLI) value was more than 60 or when ultrasonography showed evidence of a fatty liver.^[15,16] The FLI is calculated as follows:

$$\text{FLI} = (e^{0.953} \times \text{Log}_e (\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \text{Log}_e (\text{GGT}) + 0.053 \times (\text{waist circumference} - 15.745)) / (1 + e^{0.953} \times \text{Log}_e (\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \text{Log}_e (\text{GGT}) + 0.053 \times (\text{waist circumference} - 15.745)) \times 100$$

The lipid accumulation product (LAP), which is useful for the diagnosis of fatty liver, was also identified as a single variable factor.^[17] LAP was calculated as follows:

LAP = ((waist circumference - 65) $\times$ triglycerides) for men, or ((waist circumference - 58) $\times$ triglycerides) for women

All HCWs received intramuscularly administered HBV surface antigen (HBsAg) vaccinations, and all vaccinations were scheduled for 0, 1 and 6 months-post initial inoculation. After the initial 3-dose vaccination process, if the anti-HBs titer were < 10 mIU/mL, then an additional vaccine schedule was needed, and the HCW was inoculated with an additional round of vaccination. The additional vaccination schedule was also 0, 1, and 6 months.

HCWs with the following criteria were excluded: those who were HBsAg-positive, hepatitis C (HCV) antibody-positive, human immunodeficiency virus (HIV)-positive, or HBV core antibody (HBcAb)-positive; those who had anti-HBs

titers ≥ 10 mIU/mL but were vaccinated; those for whom we could not confirm their immune response

Table 1: Distribution of immune response types following anti-HBs titer measurements

	Frequency	Percentage
Type of response* ($n=213$)		
Nonresponsive	3	1.41
Hyporesponsive	25	11.74
Hyperresponsive	185	86.85

*Nonresponsive, anti-HBs titer <10 mIU/mL; hyporesponsive, anti-HBs titer between 10 and 100 mIU/mL; hyperresponsive, anti-HBs titer ≥ 100 mIU/mL

because there was no follow-up examination after the vaccination; and those who did not have information at the health checkup.

Statistical analysis

The program used for statistical analysis was Stata, version 14.0 for Windows (Stata Corporation, College Station, TX, USA). We used descriptive statistics to describe demographic characteristics of the participants. To compare the two groups, we used Pearson's Chi-squared test or Fisher's exact test for categorical data and the Mann-Whitney U test for continuous data. Associated factors of poor immune response

Table 2: Demographic characteristics of HCWs and comparison of nonresponsive and hyporesponsive groups versus hyperresponsive group

	Overall	<100 mIU/mL [†]	≥ 100 mIU/mL [‡]	P
Total HCWs	213	28 (13.2)	185 (86.8)	
Sex, n (%)				<0.001
Male	82 (38.5)	20 (71.4)	62 (33.5)	
Female	131 (61.5)	8 (28.6)	123 (66.5)	
Age, years	31.0 (28.0; 39.0)	38.0 (30.5; 44.0)	31.0 (28.0; 38.0)	0.007
Age, n (%)				0.209
<30	74 (34.7)	7 (25.0)	67 (36.2)	
30-45	113 (53.1)	15 (53.6)	98 (53.0)	
≥ 45	26 (12.2)	6 (21.4)	20 (10.8)	
Waist circumference, cm	72.0 (66.0; 80.0)	79.7 (69.5; 90.5)	71.9 (65.0; 79.0)	0.002
BMI, kg/m ²	21.7 (19.7; 23.8)	24.5 (21.1; 27.3)	21.6 (19.6; 23.2)	<0.001
BMI, n (%)				<0.001
<25	176 (82.6)	14 (50.0)	162 (87.6)	
25-30	31 (14.6)	11 (39.3)	20 (10.8)	
≥ 30	6 (2.8)	3 (10.7)	3 (1.6)	
Total cholesterol, mg/dL	178.0 (161.0; 203.0)	178.0 (164.0; 216.5)	178.0 (158.0; 200.0)	0.296
Triglyceride, mg/dL	74.0 (57.0; 109.0)	91.0 (63.0; 144.5)	72.0 (57.0; 102.0)	0.050
HDL cholesterol, mg/dL	62.0 (50.0; 71.0)	57.0 (42.5; 63.0)	63.0 (51.0; 72.0)	0.031
LDL cholesterol, mg/dL	103.0 (86.0; 128.0)	105.0 (94.0; 144.5)	102.0 (84.0; 126.0)	0.237
FLI*, n (%)				<0.001
Positive	26 (12.2)	10 (35.7)	16 (8.7)	
Negative	187 (87.8)	18 (64.3)	169 (91.3)	
LAP	9.3 (4.6; 18.5)	18.5 (5.8; 36.9)	8.9 (4.5; 17.6)	0.011
Anti-HBs titer at the beginning of employment, n (%)				0.003
≥ 10 mIU/ml	66 (31.0)	2 (7.1)	64 (34.6)	
<10 mIU/ml	147 (69.0)	26 (92.9)	121 (65.4)	
AST, IU/L	17.0 (15.0; 22.0)	19.0 (14.0; 29.5)	17.0 (15.0; 21.0)	0.325
ALT, IU/L	14.0 (10.0; 21.0)	18.5 (13.5; 29.5)	13.0 (9.0; 19.0)	0.002
ALP, IU/L	62.0 (54.0; 77.0)	65 (53.0; 91.0)	61.5 (54.0; 76.0)	0.379
GGT, IU/L	13.0 (10.0; 20.0)	20.5 (15.0; 28.5)	13.0 (10.0; 18.0)	<0.001
Albumin, g/dL	4.8 (4.5; 4.9)	4.8 (4.6; 5.0)	4.7 (4.5; 4.9)	0.234
Bilirubin (total), mg/dL	0.6 (0.4; 0.8)	0.6 (0.3; 0.8)	0.6 (0.4; 0.8)	0.383
Bilirubin (direct), mg/dL	0.2 (0.1; 0.3)	0.2 (0.1; 0.2)	0.2 (0.1; 0.3)	0.361
HbA1c, %	5.3 (5.1; 5.5)	5.4 (5.1; 5.5)	5.3 (5.1; 5.5)	0.187

Values are presented as the median (Q1; Q3) or n (%), n : number of HCWs, %: percentage, BMI: body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein, FLI: fatty liver index, anti-HBs: HBV surface antibody, LAP: lipid accumulation product, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: γ -glutamyl transpeptidase, HbA1c: hemoglobin A1c., *FLI value was more than 60 or there were liver ultrasonographic fatty liver findings, [†]the anti-HBs titers of the nonresponsive group plus the hyporesponsive group, [‡]the anti-HBs titers of the hyperresponsive group

were analyzed using logistic regression. Multivariate analysis of factors with a P value less than 0.05 was performed in a univariate analysis. $P < 0.05$ were considered statistically significant. The clinical protocol was reviewed and approved at the hospital by the Institutional Review Board (SCMC 2019-02-001).

RESULTS

Data were collected from a total of 303 HCWs, and the data from 213 HCWs were subsequently

analyzed after exclusion based on the exclusion criteria. Among 213 HCWs, 28 (13.2%) had anti-HBs titers <100 mIU/mL (hypo-responsive and nonresponsive groups) and 185 (86.8%) had anti-HBs titers ≥ 100 mIU/mL (hyperresponsive group). The results demonstrating the HBV vaccine immune responses via the HBV titers are shown in Table 1.

The demographic characteristics and comparisons between the nonresponsive and hypo-responsive groups

Table 3: Changes in the anti-HBs titers observed every year according to the type of immune response after inoculation

	Anti-HBs ≥ 10 mIU/mL, after initial vaccination [†] , n (%)	Anti-HBs <10 mIU/mL, after revaccination [‡] , n (%)	Anti-HBs ≥ 10 mIU/mL, after revaccination [§] , n (%)
Type of response*			
Nonresponsive ($n=3$)	0 (0)	3 (100)	0 (0)
Hypo-responsive ($n=25$)	7 (28)	10 (40)	8 (32)
Hyperresponsive ($n=185$)	181 (97.84)	3 (1.62)	(0.54)

n : number of HCWs, %: percentage of HCWs, anti-HBs: HBV surface antibody. *Nonresponsive, anti-HBs titer <10 mIU/mL; hypo-responsive, anti-HBs titer between 10 and 100 mIU/mL; hyperresponsive, anti-HBs titer ≥ 100 mIU/mL. [†]Those who maintained anti-HBs titers ≥ 10 mIU/mL without additional vaccination during the observation period after inoculation. [‡]Those who required an additional booster vaccination during the observation period after initial inoculation but had anti-HBs titers that remained <10 mIU/mL even after the additional inoculation. [§] Those who required an additional booster vaccination during the observation period after initial inoculation and successfully maintained anti-HBs titers ≥ 10 mIU/mL

Table 4: Univariate and multivariate analysis of factors associated with the nonresponsive and hypo-responsive groups

	Crude		Adjusted	
	OR (95% CI)	P	OR (95% CI)	P
Sex				
Male	4.96 (2.07-11.90)	<0.001	2.66 (0.95-7.42)	0.062
Female	Reference	-	Reference	-
Age	1.08 (1.03-1.13)	0.002	1.05 (0.99-1.12)	0.087
Waist circumference	1.07 (1.03-1.10)	<0.001	-	-
BMI ²	1.25 (1.12-1.41)	<0.001	-	-
Total cholesterol	1.01 (0.99-1.02)	0.305		
Triglyceride	1.01 (1.01-1.01)	0.030	-	-
HDL cholesterol	0.97 (0.94-0.99)	0.025	1.00 (0.97-1.04)	0.837
LDL cholesterol	1.01 (0.99-1.02)	0.319		
FLI*				
Positive	5.87 (2.32-14.84)	<0.001	1.01 (0.24-4.18)	0.988
Negative	Reference	-	Reference	-
LAP	1.02 (1.01-1.03)	0.007	1.01 (0.99-1.02)	0.216
Anti-HBs titer at the beginning of employment				
≥ 10 mIU/mL	Reference	-	Reference	-
<10 mIU/mL	6.88 (1.58-29.90)	0.010	6.12 (1.34-27.93)	0.019
AST	1.01 (0.98-1.03)	0.589		
ALT	1.01 (0.99-1.03)	0.194		
ALP	1.02 (0.99-1.05)	0.139		
GGT	1.00 (0.99-1.01)	0.575		
Albumin	1.11 (0.93-1.32)	0.259		
Bilirubin (total)	1.00 (0.88-1.13)	0.970		
Bilirubin (direct)	0.84 (0.53-1.34)	0.468		
HbA1c	1.09 (0.95-1.24)	0.213		

BMI: body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein, FLI: fatty liver index, anti-HBs: HBV surface antibody, LAP: lipid accumulation product, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: γ -glutamyl transpeptidase, %: percentage, *: FLI value was more than 60 or there were liver ultrasonographic fatty liver findings

versus the hyperresponsive group are described in Table 2. HCWs in the hyporesponsive and nonresponsive groups were more likely to be male (71.4% in the hyporesponsive/nonresponsive groups vs 33.5% in the hyperresponsive group, $P < 0.001$), older (38.0 vs 31.0 years, $P = 0.007$), have a higher waist circumference (79.7 vs 71.9 cm, $P = 0.002$), higher BMI (24.5 vs 21.6 kg/m², $P < 0.001$), more fatty liver (35.7% vs 8.7%, $P < 0.001$), and higher LAP values (18.5 vs 8.9, $P = 0.011$). Conversely, HBV antibody titers at the beginning of employment (7.1% vs 34.6%, $P = 0.003$) and high density lipoprotein (HDL) cholesterol (57.0 vs 63.0 mg/dL, $P = 0.031$) were lower in both the hyporesponsive and nonresponsive groups compared to the hyperresponsive group.

After vaccination, the mean time to anti-HBs follow-up was 44.6 months. After inoculation, 21 of the 28 (75.0%) HCWs in the hyporesponsive and nonresponsive group required a booster vaccination. Among these 21 HCWs, 13 (61.9%) did not maintain an anti-HBs titer above 10 mIU/mL after the booster vaccination. In the hyperresponsive group, antibody follow-up revealed that 181 of 185 (97.84%) HCWs maintained protective levels from the initial immune response and did not require additional vaccinations. Changes in anti-HBs titers were analyzed and categorized; these changes are shown in Table 3.

Multivariate analysis of the risk factors associated with the HBV vaccine in the nonresponsive and hyporesponsive groups are described in Table 4. In univariate analyses, factors found to be more significantly associated with the nonresponsive and hyporesponsive groups included being male (odds ratio (OR), 4.96; confidence interval (CI), 2.07-11.90; $P < 0.001$), being older (OR, 1.08; CI, 1.03-1.13; $P = 0.002$), having a higher waist circumference (OR, 1.07; 1.03-1.10), higher BMI (OR, 1.25; CI, 1.12-1.41; $P < 0.001$), higher triglycerides (OR, 1.01; CI, 1.01-1.01; $P = 0.030$), higher LAP (OR, 1.02; CI, 1.01-1.03; $P = 0.007$), lower HDL cholesterol (OR, 0.97; CI, 0.94-0.99; $P = 0.025$), having a fatty liver (OR, 5.87; CI, 2.32-14.84; $P < 0.001$) and having low anti-HBs titers at the beginning of employment (OR, 6.88; CI, 1.58-29.90; $P = 0.010$). After adjusting for other factors, the anti-HBs titers at the beginning of employment remained a significant factor in the logistic regression (OR, 6.12; CI, 1.34-27.93; $P = 0.019$).

DISCUSSION

Hepatitis B virus (HBV) infection is a major global health problem and high-risk groups such as HCWs are highly exposed to HBV; therefore, vaccination is recommended

in HCWs with anti-HBs titers <10 mIU/mL, regardless of previous vaccination status.^[8]

In Korea, the seroprevalence of HBV among HCWs was as follows: approximately 76.9% were positive for anti-HBs and 73.1% had anti-HBs titers ≥ 100 mIU/mL. Approximately 25% of the HCWs in this study stated that they needed to be vaccinated for HBV.^[18] Additionally, our study found that 13.2% of HCWs had a nonresponse or a hyporesponse to HBV vaccination, and 75% of these individuals received an additional booster vaccination. We investigated the immune response and potential factors associated with poor immunization response following the HBV vaccination.

Recently, the prevalence of undetectable vaccine-induced immunity in high-risk adult HBV patients was studied in the United States; despite recommendations for national vaccination for the prevention of HBV in certain high-risk groups, the prevalence of undetectable vaccine-induced immunity was not significantly different between high-risk and non-high-risk groups.^[19] The conclusions of this study indicate that immunity to HBV in high-risk groups should be improved, and a rescreening of high-risk groups may contribute to the prevention of HBV infection. In our study, HCWs, who have a high risk for HBV infection, were screened for anti-HBs titers, and our results indicated that 75% of the nonresponsive/hyporesponsive groups required revaccination. Therefore, more aggressive follow-up for hyporesponsive and nonresponsive groups in screening for anti-HBs after vaccination will help prevent HBV infection.

In our study, three (1.41%) out of 213 HCWs were nonresponsive after vaccination, all of which were revaccinated. Nevertheless, their anti-HBs titers remained less than 10 mIU/mL after revaccination. Previous studies have shown that the nonresponse rate after vaccination in adults is 5–10%.^[20] In addition, revaccination for nonresponders results in a 15–25% antibody response after one vaccination dose and a 30–50% antibody response after three vaccination doses.^[21] Perhaps the reason our study differs from previous studies is that the overall sample size was small, with a small number of nonresponders.

During the mean follow-up period of 44.6 months, the additional revaccination rate was 75% (21/28) in the HCWs with anti-HBs titers <100 mIU/mL after vaccination in our study. Among these HCWs, 13 (61.9%) did not maintain their anti-HBs titers above 10 mIU/mL after the additional vaccination. Compared to other studies, the amount of time before becoming anti-HBs-negative was shorter in this study

in the hyporesponsive and nonresponsive groups. Other previous studies reported that the rate of becoming antibody-negative after vaccination was 7–50% within 5 years and 30–60% within 10 years in adults.^[22] The results from our study showed that in HCWs, the hyporesponsive and nonresponsive groups required active follow-up after vaccination, which was 38.1% effective along with additional vaccinations. The majority of research in previous studies has focused on the nonresponsive group because the level of protective anti-HBs titers $10 \geq \text{mIU/mL}$; however, other previous studies showed that active research is needed for the hyporesponsive group.^[14,23] Therefore, in this study, the hyporesponsive and nonresponsive groups (anti-HBs titers $<100 \text{ mIU/mL}$) were compared with the hyperresponsive group (anti-HBs titers $\geq 100 \text{ mIU/mL}$) to analyze associated factors.

Our results demonstrate that low anti-HBs titers at the beginning of employment remained significantly associated with poor immune responses to vaccination in the multivariable analysis (OR, 6.12; CI, 1.34-27.93; $P = 0.019$). At the beginning of employment, if the HCW had anti-HBs titers $\geq 10 \text{ mIU/mL}$ and they were negative for HBcAb, then they had been previously vaccinated for HBV and had maintained a protective level of anti-HBs. However, in some cases, even after previously receiving an HBV vaccination, some HCWs may be negative for the antibody at the beginning of their employment; therefore, this variable does not completely represent a history of hepatitis vaccination. However, this is still a good source of information, and as those who received the HBV vaccine previously and maintained a protective level of the antibody were more likely to respond better to the additional HBV vaccination.

We tried to verify the association between the studied variables and fatty liver risk factors related to vaccination. In the AASLD 2018 Clinical Practice Guidelines, those with elevated levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of unknown etiology are classified as a high-risk group requiring HBV vaccination, and among the representative causes of abnormal liver function, fatty liver is included.^[8] In particular, nonalcoholic fatty liver is becoming an important issue for Koreans. In previous studies, the prevalence of nonalcoholic fatty liver in Koreans was found to be approximately 16.1%.^[24] Therefore, we examined the association between the immune response to HBV vaccination and fatty liver. In our study, the univariate analysis showed a significant association (OR, 5.87; CI, 2.32-14.84; $P < 0.001$), but the multivariate analysis showed no statistically significant results (OR,

1.01; CI, 0.24-4.18; $P = 0.988$). However, other studies have reported that BMI is associated with HBV vaccine immune response and with the risk of fatty liver disease.^[25-27] Therefore, the results of this study alone cannot confirm that fatty liver is not related to immune response to the HBV vaccine. In addition, a limitation of this study may be the relatively low number of subjects analyzed. More research is needed in this area.

The limitations of this study are the relatively small sample sizes and its retrospective nature. Because of how information is gathered in the retrospective study method, information was not obtained on the occupations of the HCWs, their history of HBV vaccination, drinking, or smoking, or the type of vaccination products used.

CONCLUSION

In summary, the immune response rate to the HBV vaccine among HCWs was as follows: 28 (13.2%) were classified as hyporesponsive or nonresponsive, and 185 (86.8%) were classified as hyperresponsive. The incidence of revaccination was 75% in the hyporesponsive and nonresponsive groups. In addition, the factor associated with poor immune responses was found to be an anti-HBs titer at the beginning of employment that was below the protective level. Based on this information, HCWs can be further protected from HBV if their vaccination results are explicitly discussed at postvaccination follow-ups.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Lavanchy D, Kane M. Global epidemiology of hepatitis B virus infection. *Hepatitis B Virus in Human Diseases*. Springer; 2016. p. 187-203.
2. Harpaz R, Von Seidlein L, Averbach FM, Tormey MP, Sinha SD, Kotsopoulou K, *et al.* Transmission of hepatitis B virus to multiple patients from a surgeon without evidence of inadequate infection control. *N Engl J Med* 1996;334:549-54.
3. Marković-Denić L, Branković M, Maksimović N, Jovanović B, Petrović I, Simić M, *et al.* Occupational exposures to blood and body fluids among health care workers at university hospitals. *Srp Arh Celok Lek* 2013;141:789-93.
4. Prüss-Üstün A, Rapiti E, Hutin Y. Estimation of the global burden of disease attributable to contaminated sharps injuries among health-care workers. *Am J Ind Med* 2005;48:482-90.
5. Gilca V, De Serres G, Boulianne N, Murphy D, De Wals P, Ouakki M, *et al.* Antibody persistence and the effect of a booster dose given 5, 10 or 15 years after vaccinating preadolescents with a recombinant hepatitis B vaccine. *Vaccine* 2013;31:448-51.
6. Chou R, Dana T, Bougatsos C, Blazina I, Khangura J, Zakher B. Screening for hepatitis B virus infection in adolescents and adults: A systematic review to update the US Preventive Services

- Task Force recommendation. *Ann Intern Med* 2014;161:31-45.
7. FitzSimons D, McMahon B, Hendrickx G, Vorsters A, Van Damme P. Burden and prevention of viral hepatitis in the Arctic region, Copenhagen, Denmark, 22–23 March 2012. *Int J Circumpolar Health* 2013;72:21163. doi: 10.3402/ijch.v72i0.21163.
 8. Terrault NA, Lok AS, McMahon BJ, Chang KM, Hwang JP, Jonas MM, *et al.* Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018;67:1560-99.
 9. Centers for Disease Control and Prevention. Use of hepatitis B vaccination for adults with diabetes mellitus: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2011;60:1709-11.
 10. Kim DK, Riley LE, Harriman KH, Hunter P, Bridges CB. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older—United States, 2017. *MMWR Morb Mortal Wkly Rep* 2017;66:136-8.
 11. Joukar F, Mansour-Ghanaei F, Naghipour MR, Asgharnezhad M. Immune responses to single-dose versus double-dose hepatitis B vaccines in healthcare workers not responding to the primary vaccine series: A randomized clinical trial. *Hepat Mon* 2016;16:e32799.
 12. Bruce MG, Bruden D, Hurlburt D, Zanis C, Thompson G, Rea L, *et al.* Antibody levels and protection after hepatitis B vaccine: Results of a 30-year follow-up study and response to a booster dose. *J Infect Dis* 2016;214:16-22.
 13. Haviari S, Bénet T, Saadian-Elahi M, André P, Loulergue P, Vanhems P. Vaccination of healthcare workers: A review. *Hum Vaccin Immunother* 2015;11:2522-37.
 14. McMahon BJ, Dentinger CM, Bruden D, Zanis C, Peters H, Hurlburt D, *et al.* Antibody levels and protection after hepatitis B vaccine: Results of a 22-year follow-up study and response to a booster dose. *J Infect Dis* 2009;200:1390-6.
 15. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, *et al.* The Fatty Liver Index: A simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 2006;6:33.
 16. Calori G, Lattuada G, Ragona F, Garancini MP, Crosignani P, Villa M, *et al.* Fatty liver index and mortality: The Cremona study in the 15th year of follow-up. *Hepatology* 2011;54:145-52.
 17. Bedogni G, Kahn HS, Bellentani S, Tiribelli C. A simple index of lipid overaccumulation is a good marker of liver steatosis. *BMC Gastroenterol* 2010;10:98.
 18. Shin B-M, Yoo HM, Lee AS, Park SK. Seroprevalence of hepatitis B virus among health care workers in Korea. *J Korean Med Sci* 2006;21:58-62.
 19. Yeo YH, Le MH, Chang ET, Henry L, Nguyen MH. The prevalence of undetectable vaccine-induced immunity against hepatitis B virus in US adults at high risk for infection. *Hepatology* 2019;69:1385-97.
 20. Szmunn W, Stevens CE, Zang EA, Harley EJ, Kellner A. A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B): A final report. *Hepatology* 1981;1:377-85.
 21. Poland GA. Hepatitis B immunization in health care workers. *Am J Prev Med* 1998;15:73-7.
 22. Wainwright RB, Bulkow LR, Parkinson AJ, Zanis C, McMahon BJ. Protection provided by hepatitis B vaccine in a Yupik Eskimo population—Results of a 10-year study. *J Infect Dis* 1997;175:674-7.
 23. Jack A, Hall A, Maine N, Mendy M, Whittle H. What level of hepatitis B antibody is protective? *J Infect Dis* 1999;179:489-92.
 24. Park SH, Jeon WK, Kim SH, Kim HJ, Park DI, Cho YK, *et al.* Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. *J Gastroenterol Hepatol* 2006;21:138-43.
 25. Muvunyi CM, Harelimana JDD, Sebatunzi OR, Atmaprakash AC, Seruyange E, Masaisa F, *et al.* Hepatitis B vaccination coverage among healthcare workers at a tertiary hospital in Rwanda. *BMC Res Notes* 2018;11:886.
 26. Wood RC, MacDonald KL, White KE, Hedberg CW, Hanson M, Osterholm MT. Risk factors for lack of detectable antibody following hepatitis B vaccination of Minnesota health care workers. *JAMA* 1993;270:2935-9.
 27. Zhang L, Liu J, Lu J, Yan B, Song L, Li L, *et al.* Antibody response to revaccination among adult non-responders to primary Hepatitis B vaccination in China. *Hum Vaccin Immunother* 2015;11:2716-22.