



Nonimmunity against hepatitis B virus infection in patients newly diagnosed with inflammatory bowel disease

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Background/Aims: This study aimed to elucidate the prevalence of hepatitis B virus (HBV) serologic markers in Korean patients newly diagnosed with, but not yet treated for inflammatory bowel disease (IBD). **Methods:** We prospectively enrolled 210 patients newly diagnosed with IBD (109 with ulcerative colitis and 101 with Crohn's disease). Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc) levels were measured and compared with those of 1,100 sex- and age-matched controls. **Results:** The prevalence of chronic HBV infection (positive HBsAg, positive anti-HBc, and negative anti-HBs results) and past infection (negative HBsAg, positive anti-HBc, and positive or negative anti-HBs results) were not significantly different between the patients and controls (chronic HBV infection: IBD, 3.8% vs. control, 4.9%, $P=0.596$; past infection: IBD, 26.2% vs. control, 28.8%, $P=0.625$). The patients with IBD aged <20 years were at a higher susceptibility risk (nonimmune) for HBV infection than the controls (IBD, 41.5% vs. control, 22.4%; $P=0.018$). In the multivariate analysis, an age of <20 years ($P=0.024$) and symptom duration of ≥ 12 months before diagnosis ($P=0.027$) were identified as independent risk factors for nonimmunity against HBV infection. **Conclusions:** The patients newly diagnosed with IBD were susceptible to HBV infection. The frequency of nonimmunity was high, especially in the patients aged <20 years and those with a longer duration of symptoms before diagnosis. Therefore, it is necessary to screen for HBV serologic markers and generate a detailed vaccination plan for patients newly diagnosed with IBD. (**Intest Res 2018;16:400-408**)

Key Words: Inflammatory bowel disease; Colitis, ulcerative; Crohn disease; Hepatitis B virus; Vaccination

INTRODUCTION

Worldwide, approximately 400 million individuals have been infected with HBV; HBV infection remains the most

common cause of liver cirrhosis and hepatocellular carcinoma.¹ Korea is known as an HBV infection-endemic area, and before the 1980s, its prevalence was ~8%.² Since the start of the neonatal vaccination project in 1995, the prevalence of HBV infection has dramatically decreased; recently, the prevalence in school-aged children is less than 1%.² In contrast, the current number of patients with IBD in Korea is increasing significantly.³

There has been a controversy over the prevalence of HBV infection in patients with IBD, and some recent studies have shown that there is no significant difference when it is compared with that of the general population.⁴⁻⁶ Additionally, there are some reports that even if patients with adolescent-

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or adult-onset IBD were inoculated with the HBV vaccine when they were toddlers, their antibody titers were still low during adulthood because of the effect of immunosuppressants.⁷⁻¹⁰ However, these studies have shown that low antibody titers are caused by external factors, such as drugs; IBD itself was not mentioned as a factor.

Therefore, in this study, we compared the prevalence among patients who were newly diagnosed with IBD, those who had never been treated for the disease, and the general population. Further, when these patients were diagnosed with IBD, we measured their HBV antibody levels that resulted from the inoculation with the HBV vaccine when they were toddlers.

METHODS

1. Study Design

We prospectively enrolled patients with IBD using data from the Crohn's and Colitis Association in the Daegu-Gyeongbuk registry between March 2014 and October 2015. We analyzed patients newly diagnosed with IBD; those not screened for HBV were excluded. All diagnoses of IBD were made on the basis of a detailed clinical history, close physical examination findings, laboratory data, and a combination of radiologic, endoscopic, and histological findings. At the time of diagnosis, a blood sample was collected from each patient for the evaluation of HBV infection markers. The study was approved by the ethics committee of the institutional review boards of the 7 tertiary referral medical centers conducting the research, and informed consent was obtained from each patient.

2. Patients and Viral Serologic Markers

From March 2014 to October 2015, 210 patients newly diagnosed with IBD (101 with CD and 109 with UC) were enrolled in our study. HBsAg, anti-HBc, and anti-HBs levels were evaluated in all 210 patients. Demographic and clinical characteristics, including age at the time of IBD diagnosis, symptom duration before diagnosis, and sex, were documented for the examination of possible risk factors for nonimmunity (defined as anti-HBs level of <10 mIU/mL, anti-HBc negativity, and HBsAg negativity) against HBV infection. A total of 1,100 individuals who visited the Health Medical Examination Center of Keimyung University Hospital, Daegu, Korea from March 2014 to September 2015 for a routine health examination were included as healthy controls. The number of the sex- and age-matched controls was

five times higher than that of the patients newly diagnosed with IBD. All patients completed a questionnaire regarding their medical and personal history; those diagnosed with IBD were excluded. Because the prevalence of HBV infection in younger adults is dramatically decreasing because of the implementation of the HBV neonatal vaccination strategy in 1995,¹¹ our study divided the patients with IBD into 3 subgroups, according to age at the time of diagnosis: <20, 20–44, and ≥45 years. We then compared the prevalence of HBV infection serologic markers (HBsAg, anti-HBs, and anti-HBc) by subgroup. These markers were analyzed using a chemiluminescent immunoassay method (ADVIA Centaur, Siemens Health Care Diagnostics Inc., Tarrytown, NY, USA).

3. Definitions

Past and present HBV infections were defined on the basis of the terminology applied by the National Institutes of Health's conferences on the management of hepatitis B.¹² Past HBV infection was defined as anti-HBc positivity with or without anti-HBs. Present HBV infection was defined as the existence of HBsAg. Effective vaccination was defined as an anti-HBs level of ≥10 mIU/mL, HBsAg negativity, and anti-HBc negativity. Nonimmunity was defined as an anti-HBs level of <10 mIU/mL, HBsAg negativity, and anti-HBc negativity.¹³

4. Statistical Analysis

Categorical variables were analyzed using Fisher exact test or the chi-square test. Continuous variables were examined using Student *t*-test. The results were expressed as means with SDs or medians with interquartile ranges (IQRs). A multivariate analysis of the independent risk factors for nonimmunity was performed using binary logistic regression after the identification of appropriate risk factors that presented significant correlations ($P < 0.1$) in the univariate analysis. Two-tailed P -values of <0.05 were considered statistically significant. The statistical analysis was performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Demographic and Clinical Characteristics of the Patients Newly Diagnosed with IBD

Patient age at the time of CD diagnosis was significantly lower than that at the time of UC diagnosis (26.6±12.5 years

vs. 42.7 ± 18.0 years, $P < 0.001$). The symptom duration before diagnosis was longer in the patients with CD than in those with UC (17.4 ± 32.6 months vs. 10.6 ± 24.7 months, $P < 0.001$). The clinical characteristics of the patients with IBD according to Montreal classification are shown in Table 1.

Table 1. Clinical Characteristics of the Patients with IBD

Characteristics	CD (n=101)	UC (n=109)	P-value
Age at diagnosis (yr)	26.6 ± 12.5	42.7 ± 18.0	<0.001
Symptom duration before diagnosis (mo)	17.4 ± 32.6	10.6 ± 24.7	<0.001
Male sex	74 (73.2)	59 (54.1)	0.007
CD location			
L1 (terminal ileum)	28 (27.7)		
L2 (colon)	35 (34.7)		
L3 (ileocolonic)	38 (37.2)		
L4 (upper GI)	3 (2.9)		
CD behavior			
B1 (inflammatory)	68 (67.3)		
B2 (stricturing)	18 (17.8)		
B3 (penetrating)	15 (14.9)		
Perianal disease	21 (20.8)		
UC extent			
E1 (proctitis)		38 (34.9)	
E2 (left-sided)		31 (28.5)	
E3 (extensive)		40 (36.6)	

Values are presented as mean \pm SD or as number (%). GI, gastrointestinal.

2. Proportion of the HBV Infection Statuses between the Patients and Controls

The proportion of the HBV infection statuses between the patients and controls is shown in Table 2. No significant difference in the prevalence of chronic HBV infection (positive HBsAg, positive anti-HBc, and negative anti-HBs results) was noted between the patients and controls (IBD, 3.9% [CD, 1.0%; UC, 6.5%] vs. control, 4.8%; $P = 0.596$). The prevalence of past infection (negative HBsAg, positive anti-HBc, and positive or negative anti-HBs results) was not significantly different between the patients and controls (IBD, 25.2% [CD, 25.7%; UC, 24.7%] vs. control, 27.7%, $P = 0.625$). Effective vac-

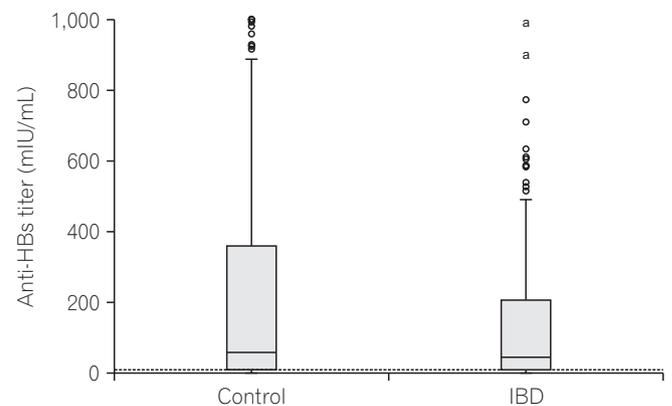


Fig. 1. Quantitative anti-HBs titer of the patients with IBD and controls. The median titer of the patients with IBD was 44.20 mIU/mL (interquartile range [IQR], 11.19–209.51 mIU/mL), and that of the controls was 59.00 mIU/mL (IQR, 8.00–360.83 mIU/mL) ($P = 0.031$). The horizontal dot bar indicates the mean cutoff value of 10 mIU/mL. The IBD group mean very high level of titers.

Table 2. Proportion of the HBV Infection Statuses between the Patients and Controls

	CD (n=101)	UC (n=109)	IBD (n=210)	Control (n=1,100)	P-value ^a
Chronic HBV infection ^b	1.0	6.5	3.9	4.8	0.596
Past infection ^c	25.7	24.7	25.2	27.7	0.625
Effective vaccination ^d	38.6	38.5	38.5	48.0	0.013
Nonimmunity ^e	34.7	30.3	32.4	19.5	<0.001

Values are presented as percentages.

^aIBD vs. control.

^bChronic HBV was defined as HBsAg positivity, anti-HBc positivity, and anti-HBs negativity.¹³ CD vs. UC, $P = 0.067$; CD vs. control, $P = 0.080$; UC vs. control, $P = 0.489$.

^cPast infection was defined as HBsAg negativity, anti-HBc positivity, and anti-HBs negativity or positivity.¹³ CD vs. UC, $P = 0.885$; CD vs. control, $P = 1.000$; UC vs. control, $P = 0.768$.

^dEffective vaccination was defined as HBsAg negativity, anti-HBc negativity, and anti-HBs level of ≥ 10 mIU/mL.¹³ CD vs. UC, $P = 1.000$; CD vs. control, $P = 0.029$; UC vs. control, $P = 0.044$.

^eNonimmunity was defined as HBsAg negativity, anti-HBc negativity, and anti-HBs level of < 10 mIU/mL.¹³ CD vs. UC, $P = 0.556$; CD vs. control, $P = 0.001$; UC vs. control, $P = 0.020$.

ination (negative HBsAg and negative anti-HBc results and anti-HBs level of ≥ 10 mIU/mL) was identified in 38.5% of the patients with IBD (CD, 38.6%; UC, 38.5%), which was significantly lower than that of the control group (48.0%, $P=0.013$). However, there was no statistically significant intergroup difference regarding the effective vaccination rates when

the patients were divided into those with UC and those with CD (Table 2). Nonimmunity against HBV infection (negative HBsAg and negative anti-HBc results and anti-HBs level of < 10 mIU/mL) was detected in 32.4% of the patients (CD, 34.7%; UC, 30.3%) compared with that in 19.5% of the controls ($P<0.001$). The quantitative anti-HBs titer of the patients

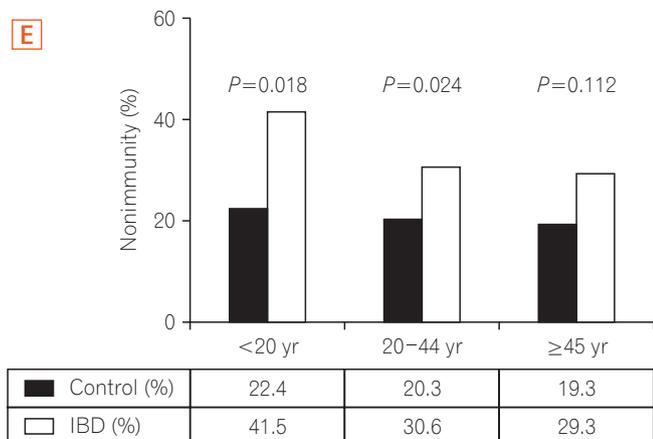
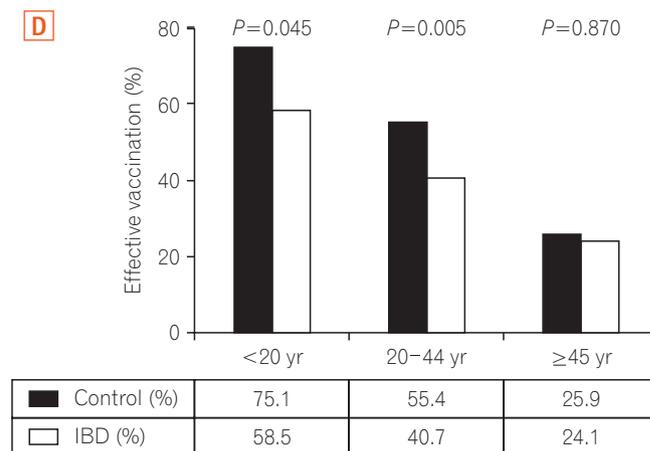
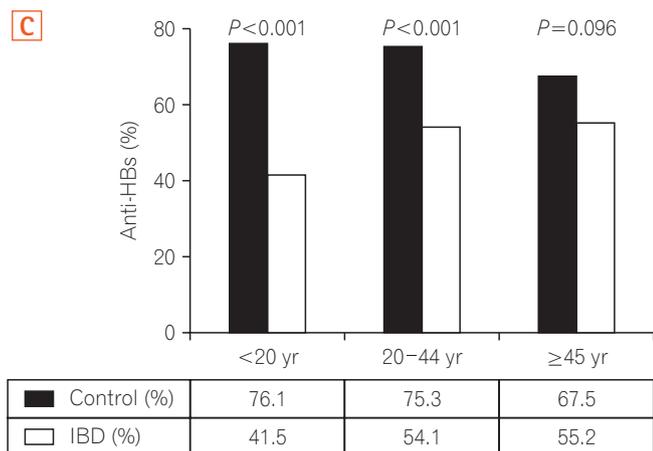
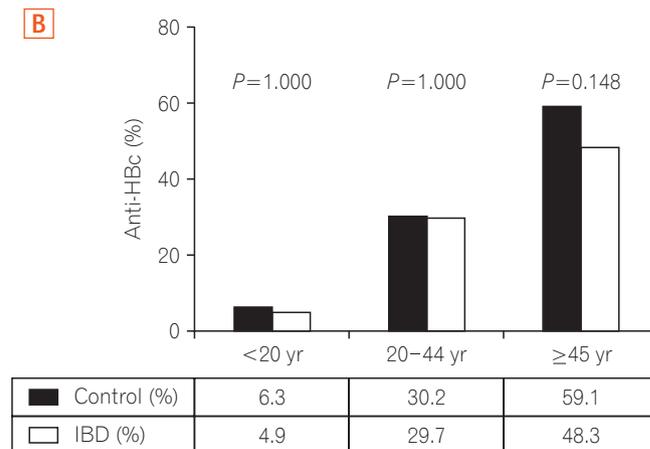
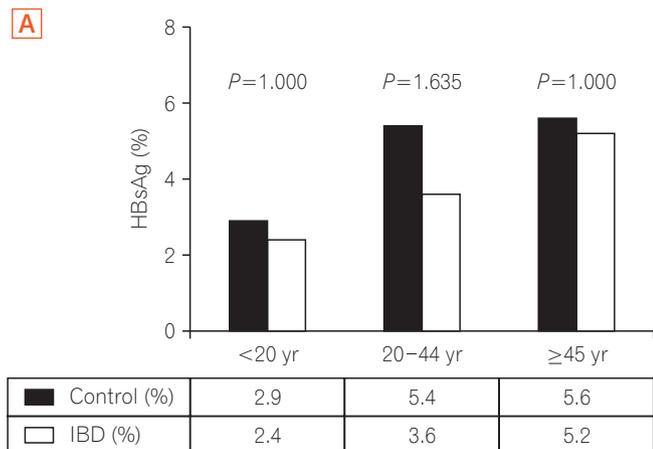


Fig. 2. Prevalence of HBV infection serologic markers by age at the time of diagnosis. (A) HBsAg; (B) anti-HBc; (C) anti-HBs; (D) effective vaccination; (E) nonimmunity.

with IBD and controls is shown in Fig. 1. The median titer of the patients with IBD was 44.20 mIU/mL (IQR, 11.19–209.51 mIU/mL), and that of the controls was 59.00 mIU/mL (IQR, 8.00–360.83 mIU/mL) ($P=0.031$). Further, the cutoff value was 10 mIU/mL as indicated by the horizontal dot bar in Fig. 1.

3. Prevalence of HBV Infection Serologic Markers by Age at the Time of Diagnosis

When the patients were divided into the 3 age-based subgroups (<20, 20–44, and ≥ 45 years), the prevalence of HBsAg positivity and anti-HBc positivity did not differ between the patients and controls regardless of age (Fig. 2A and B). However, anti-HBs positivity was noted significantly less frequently in the patients newly diagnosed with IBD than in the controls in the <20 years (IBD, 41.5%; control, 76.1%; $P<0.001$) and 20–44 years (IBD, 54.1%; control, 75.3%, $P<0.001$) subgroups, while no marked difference was seen in the ≥ 45 years subgroup (Fig. 2C). Effective vaccination was significantly less common in the patients newly diagnosed with IBD than in the controls in the <20 years (IBD, 58.5%; control, 75.1%; $P=0.045$) and 20–44 years subgroups (IBD, 40.7%; control, 55.4%; $P=0.005$); conversely, there was no meaningful difference between the patients and controls in the ≥ 45 years (IBD, 24.1%; control, 25.9%; $P=0.870$) subgroup (Fig. 2D). Nonimmunity against HBV infection was

more frequent in the patients newly diagnosed with IBD than in the controls in the <20 years (IBD, 41.5%; control, 22.4%; $P=0.018$) and 20–44 years (IBD, 30.6%; control, 20.3%; $P=0.024$) subgroups; there was no statistically significant difference between the patients newly diagnosed with IBD and controls in the ≥ 45 years subgroup (IBD, 29.3%; control, 19.3%; $P=0.112$) (Fig. 2E).

4. Risk Factors for Nonimmunity against HBV Infection in the Patients Newly Diagnosed with IBD

The univariate and multivariate analyses findings are shown in Table 3. Nonimmunity was significantly correlated with the age of <20 years at the time of diagnosis ($P=0.016$) and symptom duration of ≥ 12 months before diagnosis ($P=0.035$). Age of <20 years (OR, 2.589; 95% CI, 1.134–5.909; $P=0.024$) and symptom duration of ≥ 12 months before diagnosis (OR, 2.077; 95% CI, 1.085–3.977; $P=0.027$) were the independent risk factors for nonimmunity against HBV infection in the multivariate analysis. However, sex and IBD type were not correlated with nonimmunity.

DISCUSSION

To our knowledge, the current study is the first to assess the prevalence of HBV infection serologic markers and im-

Table 3. Univariate and Multivariate Analyses of the Risk Factors for Nonimmunity (Anti-HBs Level of <10 mIU/mL and Anti-HBc and HBsAg Negativity) to HBV Infection in the Patients with IBD

Characteristics	Univariate analysis			Multivariate analysis	
	Nonimmunity (n=90) ^a	Immune or exposed (n=120) ^b	P-value	OR (95% CI)	P-value
Age at diagnosis (yr)			0.016		
<20	24 (26.7)	17 (14.2)		2.589 (1.134–5.909)	0.024
20–44	45 (50.0)	63 (52.5)		1.280 (0.603–2.308)	0.630
≥ 45	21 (23.3)	40 (33.3)		1	
Sex			0.785		
Male	56 (62.2)	76 (63.3)			
Female	34 (37.8)	44 (36.7)			
Symptom duration (mo)			0.035		
≥ 12	31 (34.4)	24 (20.0)		2.077 (1.085–3.977)	0.027
<12	59 (65.6)	96 (80.0)		1	
Disease			0.372		
CD	47 (52.2)	54 (45.0)			
UC	43 (47.8)	66 (55.0)			

Values are presented as number (%).

^aAnti-HBs level of <10 mIU/mL and anti-HBc and HBsAg negativity.

^bAnti-HBs level of ≥ 10 mIU/mL or anti-HBc positivity.

immune status against HBV infection in patients newly diagnosed with IBD; we also compared patients with sex- and age-matched healthy controls. Two studies in Italy and Brazil reported that the HBsAg-positivity rates were significantly higher in patients with IBD than in the general population.^{14,15} However, other studies from France, Italy, Spain, and Korea reported that the HBsAg-positivity rates in patients with IBD were not significantly different from those in controls.^{4,5,16,17}

The prevalence of HBV infection markers in patients newly diagnosed with IBD in our study was considerably higher than that reported from Western studies. For example, a multicenter study of patients with IBD in Spain presented a 0.6% HBsAg-positivity rate and a 7.1% anti-HBc-positivity rate.⁴ Our study reported a 3.8% HBsAg-positivity rate and a 30.0% anti-HBc-positivity rate in Korean patients newly diagnosed with IBD, which were higher than those reported by the previous study.⁴ Other Korean IBD studies presented HBsAg-positivity rates of 3.7% and 4.1%, similar to those of this study.^{16,18} Our study demonstrated no significant difference in the HBsAg-positivity rate between the patients newly diagnosed with IBD and the general population of Korea, an HBV infection-endemic country. This result supported the data from recent studies conducted in Western countries, suggesting that IBD is no longer a risk factor for HBV infection.⁴⁻⁶

A comparable prevalence of HBV infection serologic markers in patients with IBD in Western countries has been reported.^{4,5} In our study, the positivity rate of anti-HBc, an indicator of previous HBV exposure, was similar with that of a previous study.¹⁹ When the patients newly diagnosed with IBD were divided into 3 subgroups by their age at the time of diagnosis, the anti-HBc-positivity rate increased with age. However, there was no significant difference between the patients with IBD and the controls, indicating that HBV exposure depends highly on the patient's age at the time of diagnosis. An analysis of HBV infection markers in Korean individuals showed that the anti-HBc-positivity rate decreased meaningfully with a younger age,¹⁹ a pattern similar to that of our data. Our study findings were influenced by the nationwide prophylactic HBV vaccination of neonates implemented in Korea in 1995. A Japanese study²⁰ compared viral markers of hepatitis B in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The anti-HBc-positivity rate in RA was ~25.6%, and that in SLE was ~14.2%. In contrast to the 12.2% anti-HBc-positivity rate of the control group in other studies in Japan,²¹ there was no significant difference in SLE; however, that in RA had a dif-

ference. They reported that the reason is that patients with RA are relatively older than patients with SLE. Our study also showed that the anti-HBc-positivity rate increases with age.

Our study found that the vaccination effectiveness in the patients newly diagnosed with IBD was significantly lesser than that in the controls. Many studies have presented that immunosuppressant use reduces HBV vaccination efficacy.⁷⁻¹⁰ However, the patients in this study were newly diagnosed with and not yet treated for IBD, and the vaccination effectiveness results were similar to those in another study.¹⁸ He et al.²² opposed that HBV infection in patients with IBD could worsen when treated with immunosuppressants; their finding was concordant with those of this study. We also found that the vaccination effectiveness rate was significantly lower in the subgroup of patients newly diagnosed with IBD aged <20 years than in the age-matched controls (IBD, 58.5% vs. control, 75.1%, $P=0.045$). We did not compare the vaccination rates between the patients and controls; however, we can assume that the vaccination rate of the <20-year subgroup would be higher than that of the other subgroups because of the nationwide vaccination strategy. Therefore, it appears that the lower vaccination effectiveness rate in the patients newly diagnosed with IBD was because of reasons other than the vaccination rate and use of immunosuppressants. One possible explanation for this might be a confused immune response. Cellular immune responses initiated by Type 1 helper T cells, cytokines, and regulatory T (Treg) cells effectively protect against and downregulate inflammation in human studies and animal models of CD.²³ HBV infection is also thought to cause an unusual cell-mediated immune response, and it has been proven that Treg cells are an important prognostic factor of HBV infection.²⁴ However, these hypotheses should be investigated in future research studies; nevertheless, Treg cells seem to affect both HBV infection and IBD; thus, HBV infection is likely to influence the pathogenesis of IBD and vice versa. Therefore, the aberrant immune response in patients with IBD can cause a disturbance in the HBV vaccine response.^{25,26}

One of the significant findings of our study was that non-immunity to HBV infection makes patients newly diagnosed with IBD significantly susceptible to such an infection. The nonimmunity rate was quite prominent in the subgroup of patients newly diagnosed with IBD who were aged <20 years compared with that in the controls (IBD, 41.5%; controls, 22.4%; $P=0.018$) and was statistically significant in the patients with IBD aged 20–44 years compared with that in the controls (IBD, 30.6%; control, 20.3%; $P=0.024$). In the multivariate analysis, age of <20 years and symptom dura-

tion of ≥ 12 months before diagnosis were identified as the independent risk factors for nonimmunity. Previous studies have reported that chronic liver disease, chronic kidney disease, and human immunodeficiency virus infection reduce the efficacy of HBV vaccination.²⁷⁻²⁹ However, no other study mentioned IBD as a risk factor for HBV infection. To our knowledge, this is the first study to analyze the symptom duration as a risk factor for HBV infection. These results may explain the aberrant immune response seen in patients with IBD.^{25,26}

The current study has some limitations. First, we did not check the HBV DNA levels of the patients with negative HBsAg and positive anti-HBc results. Thus, we did not measure the occult HBV levels. Patients with positive anti-HBc results are at a risk of occult HBV infection, which is a reactivation indicator particularly in those treated with chemotherapy or immunosuppressants.³⁰⁻³² In fact, immunosuppressant use is the main cause of HBV infection reactivation in patients with IBD.^{30,31} Many patients with IBD use long-term immunosuppressants, and their immune status is usually low, increasing their susceptibility to conditions, such as tuberculosis, cytomegalovirus colitis, and HBV infection reactivation. Therefore, occult HBV infection reactivation is an important potential outcome to consider in these patients, especially in Korea, an HBV infection-endemic country.³²⁻³⁷ Therefore, further studies that would explore occult HBV infection in patients with IBD need to be conducted. However, at approximately 0.016%, the prevalence of occult HBV infection in Korea is very low.³⁸ Second, our study was performed in Daegu-Gyeongbuk, a southeastern local area of Korea; however, its prevalence of HBV infection is similar to the mean rate in the country (overall country, 4.0%; Daegu, 4.2%; Gyeongbuk, 3.9%).³⁹ Our study compared the patient group with a control group, which had a five times higher number of patients, and identified a prevalence rate similar to that of a nationwide study.

In conclusion, the current study is the first to compare the prevalence of HBV infection serologic markers between patients newly diagnosed with IBD and controls, and we found that the prevalence of HBsAg positivity in the patients newly diagnosed with IBD was not significantly different from that of the general population of Korea. The vaccination efficacy was markedly lesser in the patients with IBD aged < 20 years at the time of diagnosis than in the controls. Of note, age of < 20 years and symptom duration of ≥ 12 months before diagnosis were the independent risk factors for nonimmunity. Thus, the investigation of the HBV vaccination status of young patients and those with a longer symptom duration at

the time of IBD diagnosis is important. Finally, the continued enforcement of a detailed national vaccination plan in Korea, an HBV infection-endemic country, is needed.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION

Seong Jae Yeo contributed to analysis and interpretation of data, and writing and revising the manuscript. Hyun Seok Lee contributed to concept and design of the study and reviewing the manuscript. Byung Ik Jang contributed reviewing and intellectual content of the article. All authors contributed to acquisition of data and approved the final version of the manuscript for submission.

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